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Chemotaxonomy and pharmacology of Gentianaceae

S. R. JENSEN AND J. SCHRIPSEMA

Gentianaceae -
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Struwe, L. & Albert
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University Press)
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ABSTRACT

The occurrence of taxonomically informative types of compounds in the family Gentianaceae, namely iridoids, xanthonenes, mangiferin, and C-glucoflavones, has been recorded. The properties, biosynthesis, and distribution of each group of compounds are described. The iridoids (mainly secoiridoid glucosides) appear to be present in all species investigated, with a predominance of swertiamarin and/or gentiopicroside; c. 90 different compounds have been reported from 127 species in 24 genera. Xanthonenes are not universally present in Gentianaceae, but about 100 different compounds have been reported from 121 species in 21 genera. A coherent theory for the biosynthesis of xanthonenes, based partly on published biosynthetic results and partly on biosynthetic reasoning, is postulated and used to group the compounds into biosynthetic categories. Arranging the genera according to the xanthonenes present gives rise to four groups. Group 1 (*Anthocleista*, *Blackstonia*, *Gentianopsis*, *Macrocarpaea*, and *Orphium*) includes the taxa containing only few and biosynthetically primitive xanthonenes. Group 2 (*Comastoma*, *Gentiana*, *Gentianella*, *Lomatogonium*, *Swertia*, and, tentatively, *Tripterospermum*) contains xanthonenes with an intermediate degree of biosynthetic advancement. Group 3 (*Frasera*, *Halenia*, and *Veratrum*) has the most advanced compounds, with the xanthonenes found in group 2 being the biosynthetic precursors. Group 4 (*Canscora*, *Centaurium*, *Chironia*, *Eustoma*, *Hopaea*, *Ixanthus*, and, with some reservation, *Schultesia*) contains another set of biosynthetically advanced compounds. A comparison of the above groups with strict consensus trees based on molecular data (*trnL* intron and *matK* sequences) and the new classification proposed by Struwe *et al.* (2002)

shows very good correlation. On the evidence so far, members of the Exaceae do not contain xanthonenes. The taxa of group 1, with primitive xanthonenes, are found in several tribes (Chironieae, Gentianeae, Helieae, and Potalieae), while those of groups 2 and 3 comprise solely members of the Gentianeae. Finally, the taxa in group 4 are all members of the Chironieae. Mangiferin, a C-glucoxanthone with a biosynthesis different from the above xanthonenes, has been recorded from 42 species in seven genera. Of these, five belong to the Gentianeae and two to the Chironieae. The C-glucocoflavones have been recorded from 78 species in nine genera. Three of these belong to the Potalieae, while the remaining six are members of the Gentianeae. Based on the above results, a tentative list of chemical characteristics for the tribes of the Gentianaceae is presented. Finally, some pharmacologically interesting properties of plant extracts or compounds from taxa within Gentianaceae are listed.

Keywords: biosynthesis, chemotaxonomy, Gentianaceae, pharmacology, secoiridoids, xanthonenes.

INTRODUCTION

The Gentianaceae contains many species with interesting phytochemical properties. They have been widely used in traditional medicine and also as constituents in bitters and similar concoctions. For this reason a considerable amount of chemical work has been performed on members of the family. In order to limit the information to the taxonomically most promising groups of compounds, we have concentrated our efforts on listing only the iridoids, the xanthonenes, mangiferin, and the C-glucocoflavonoids, which are most characteristic for the family.

IRIDIDS

The iridoids are a group of natural products belonging to the terpenoids, which are otherwise ubiquitous in plants. However, only a limited number of taxa possess the enzyme(s) that give rise to the cyclopentane ring that is characteristic for the carbocyclic iridoids. In plants, iridoids are usually found as glucosides and thus they are basically water soluble.

The distribution of iridoids has been shown to have considerable value as a systematic character (Jensen *et al.*, 1975; Jensen, 1991, 1992) since they occur almost exclusively in the superorders Cornanae, Ericanae, Gentiananae, and Lamianae *sensu* Dahlgren (1989). Furthermore, two different principal

biosynthetic pathways exist (Jensen, 1991). One route leads from iridodial via deoxyloganic acid and loganin or loganic acid to secoiridoids and eventually to the complex indole alkaloids (Fig. 6.1). This route is found mainly in the Gentiananae and Cornanae, but never in the Lamianae. The other route, from the 8-epimeric precursor *epi*-iridodial via *epi*-deoxyloganic acid to aucubin and similar decarboxylated compounds, is found mainly in Lamianae, but never in Gentiananae.

Approximately 1200 different iridoids and secoiridoids (not counting the complex indole alkaloids) are known so far. At about the time we were finishing this chapter, a review on iridoids and secoiridoids in the Gentianaceae appeared (Rodriguez *et al.*, 1998).

Biosynthesis

The iridoid glucosides of Gentianaceae are usually secoiridoids. The carbocyclic iridoids reported from the family are almost exclusively derivatives of loganin, the obligatory biosynthetic precursor of the secoiridoids. The few exceptions from this will be commented on later. Their biosynthesis (Fig. 6.1; bold numbers in the following text refer to the compounds drawn in the figures and are used synonymously with the compound names) was well investigated during the period 1967–1976 (see Takeda & Inouye, 1976), perhaps mainly because of the interest in the complex indole alkaloids found in related families within the order Gentianales. These compounds are derived from secologanin and are therefore, at least biosynthetically, also secoiridoids.

Early work established the terpenoid origin of the gentianaceous iridoid glucosides. Thus, feeding ^{14}C -labeled mevalonate (MVA; in Fig. 6.1 shown as mevalonolactone) to *Swertia caroliniensis* gave incorporation into gentiopicroside (**7**; Coscia & Guarnaccia, 1967). Inouye *et al.* (1967, 1970) simultaneously showed incorporation of mevalonolactone into **7** in *Gentiana triflora* and into sweroside (**5**) and swertiamarin (**6**) in *Swertia japonica*. Since the incorporation into **5** was ten times higher than that into **6**, the former was suggested to be a precursor of the latter. Further proof for the terpenoid pathway was found by incorporation of geranyl pyrophosphate into loganic acid (**2**), also a constituent of *Swertia caroliniensis* (Coscia & Guarnaccia, 1968), although it was not incorporated into gentiopicroside (**7**). This negative result was ascribed to dilution into the pool of **2** within the plant.

Next, it was established that **2** was an intermediate in the formation of **7** (Coscia *et al.*, 1969, 1970; Guarnaccia *et al.*, 1969). This was simultaneously

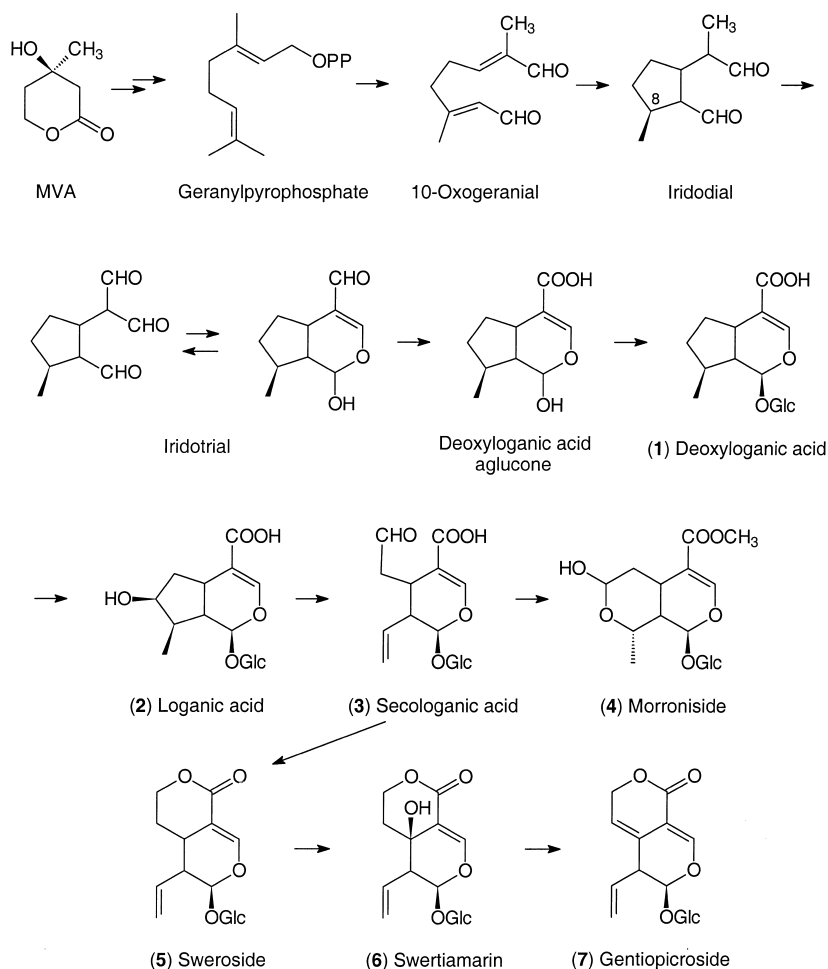


Figure 6.1. The biosynthetic pathway leading to the iridoid glucosides commonly found in Gentianaceae. MVA, mevalonolactone.

proved in *Gentiana triflora* by other groups (Inouye *et al.*, 1969, 1974a) and also in *Swertia petiolata* (Gröger & Simchen, 1969). Inouye's group later prepared labeled sweroside (5) and proved that this was also an intermediate for 7 in *Gentiana scabra* (Inouye *et al.*, 1971a).

The biosynthesis of morroniside (4), a constituent of *Gentiana thunbergii*, has also been investigated, and both loganic acid (2; Inouye *et al.*, 1974a) and deoxyloganic acid (1; Inouye *et al.*, 1976) have been shown to be precursors for 4 in this plant.

In several plant species from families other than the Gentianaceae, the pathway from MVA up to deoxyloganic acid has been established to be as shown in Fig. 6.1 (Inouye & Uesato, 1986; Jensen, 1991). Regarding the intermediacy of secologanic acid (**3**), this compound is a likely intermediate between **2** and **4**, but this has not yet been proved. Another uncertainty is the step between **2** and **3**, where the mechanism is still not understood.

The compound gentioside (**2u**; see Fig. 6.2), isolated from several species of *Gentiana* by Popov and Marekov (1971a), was also prepared in radioactive form by feeding ^{14}C -carbon dioxide to *G. asclepiadea* and isolating the compound. Using the labeled **2u** as a precursor, incorporation into gentiopicroside (**7**) was attained. However, the detailed mechanism for the conversion of deoxyloganic acid into the secoiridoids, with retention of both a C-7 and the C-8 proton, makes it highly unlikely that a compound such as **2u** without any proton at C-8 could be an intermediate in the biosynthesis (Takeda & Inouye, 1976). Furthermore, the structure given for gentioside is still somewhat doubtful because of the lack of complete NMR data for the compound.

Results

In the present work, we have classified the compounds according to biosynthetic complexity and displayed the derivatives of loganin (**2–2v**) in Fig. 6.2, those of secologanic acid and secologanol (**3–3r**) in Fig. 6.3, etc. The majority of the compounds are esters (at one or more hydroxyl groups) of the parent compound, signified by the presence of one or more ($\text{R}^1\text{--R}^5$)-groups in the derivatized oxygen atom(s). In each figure, the carboxylic acid moieties of the esters ($\text{R}^n = \text{A to S}$) are specified in a list next to the parent compound. Finally, the trivial name of each individual compound is listed in the figures.

The carbocyclic iridoids reported from the family are shown in Fig. 6.2. Some of the compounds are strictly derivatives not of loganin (**2**), but rather of its precursor deoxyloganin (**1**), so we have included three derivatives of 7-*epi*-loganin (**2p–2r**) together with gentioside (**2u**) and dihydrocornin (**2v**). Formally, the decarboxylated compounds reported from the roots of the Himalayan *Gentiana kurroo* (Sarg *et al.*, 1990, 1991) could also be included here. These compounds are aucubin and catalpol as well as a number of derivatives of the latter. However, it seems clear that this is a case of confusion with regard to the plant material used for the investigation, since other workers (Inouye & Nakamura, 1971b) isolated only the compounds morroniside (**4**) and gentiopicroside (**7**) from this species. Furthermore, *Picrorhiza*

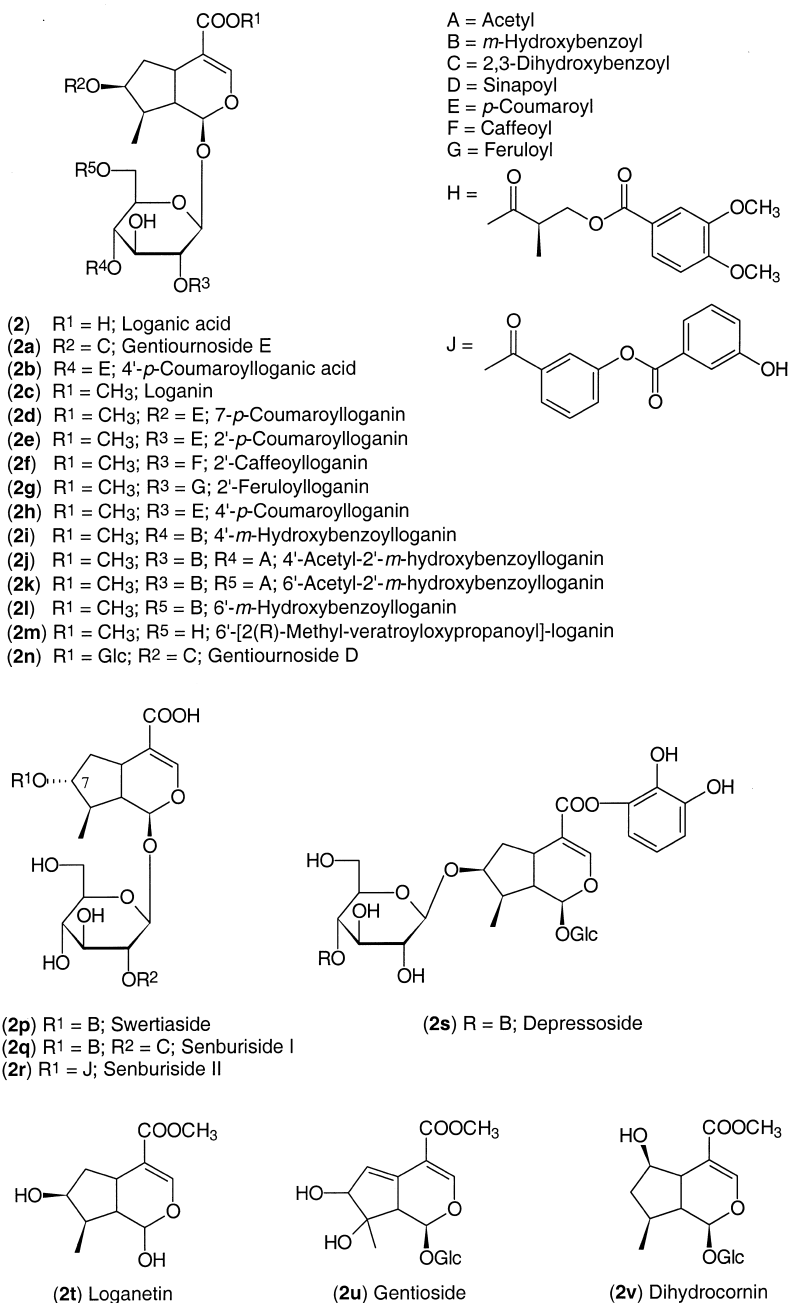


Figure 6.2. Carbocyclic iridoids of Gentianaceae, mainly loganic acid (2) and loganin (2c) and their ester derivatives.

kurrooa (Scrophulariaceae), also a Himalayan species the roots of which are much used in Chinese medicine, has been reported (Weinges *et al.*, 1972; Stuppner & Wagner, 1989) to contain the catalpol esters noted by Sarg *et al.* (1990). Finally, a report of harpagoside, an ester of the decarboxylated iridoid harpagide, from *Gentiana macrophylla* (Liu *et al.*, 1994a) seems rather unlikely, and other workers who investigated the plant (Wang & Lou, 1988; Kondo & Yoshida, 1993) did not report its presence.

The compounds derived from secologanic acid (**3**) and secologanol (**3g**) are listed in Fig. 6.3. Secologanic acid exists as an equilibrium mixture of the two forms shown, depending on the solvent. When a plant extract containing **3** is chromatographed on silica gel with solvent systems containing methanol, it is our experience that the two epimers of vogelioside (strictly C-7 epimers, but both depicted as **3a**) are readily formed. We therefore presume that vogelioside and *epi*-vogelioside are artifacts. The same is likely to be the case for the dioxolanylsecologanin (**3e**).

Iridoid glucosides derived from the hemiacetal morroniside (**4**) and the corresponding lactone, kingside (**4c**), are only occasionally reported from Gentianaceae. Those known so far are listed in Fig. 6.4.

Compounds from the biosynthetic sequence sweroside (**5**), swertiamarin (**6**), and gentiopicroside (**7**), together with their derivatives, are the most characteristic iridoids from Gentianaceae. Also in this group is present a wealth of esters, in particular as derivatives of sweroside. The compounds derived from **5–7** are listed in Figs. 6.5–6.7.

Some monoterpene alkaloids have been reported from Gentianaceae and these deserve special mention. Alkaloids are relatively easy to isolate from plant material because of their alkaline properties. Thus, when partitioning the crude extract between dilute aqueous acid and an organic solvent, the alkaloids are found as salts only in the aqueous phase, together with other water-soluble constituents such as sugars, glycosides, etc., while most other organic compounds are removed in the organic solvent. The next preparative step is addition of a base to the aqueous phase to render the alkaloids insoluble in the alkaline water but now extractable by an organic solvent. After such a separation, a fraction consisting only of alkaloids is obtained – in principle, at least. However, by similar treatment of a plant extract containing iridoid glucosides, these compounds will to some degree be hydrolyzed in the acidic medium, particularly by standing, to yield dialdehydes. Until recently, ammonia was the preferred alkaline reagent since it is mild in action. But ammonia and dialdehydes react to form dihydropyridines, which, depending on the structure of the latter, may convert spontaneously to pyridines, which are more stable. These

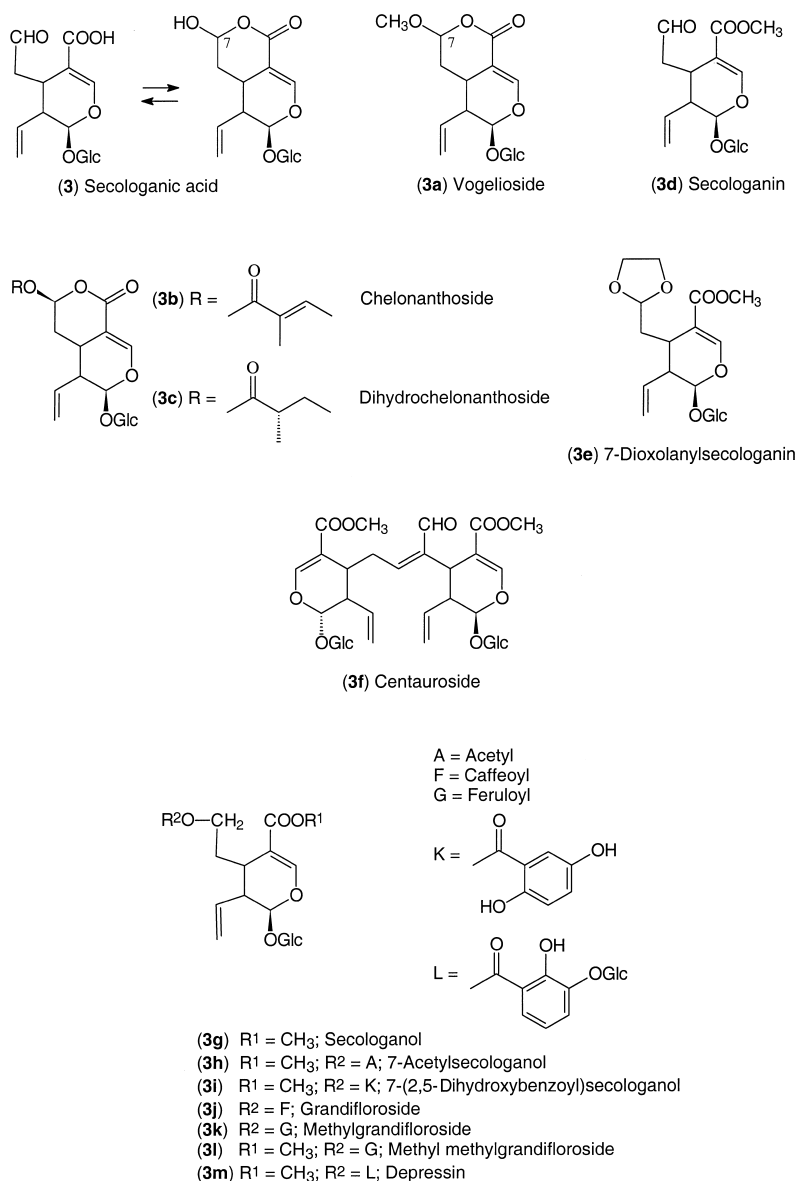
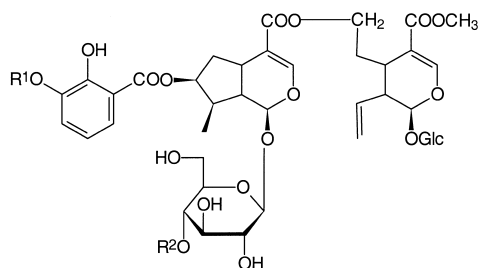
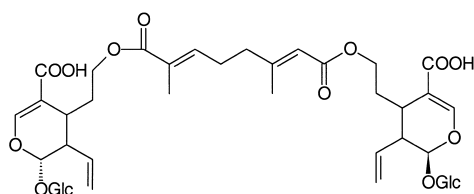


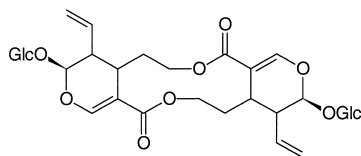
Figure 6.3. Secoiridoids of Gentianaceae: glucosides derived from secologanic acid (3) and secologanol (3g).



(3n) Depresteroside (Gentiurnoside A)

(3o) R¹ = Glu; Gentiurnoside B(3p) R² = Glu; Gentiurnoside C

(3q) Rhodenthoside A



(3r) Lisianthoside

compounds are impossible to distinguish from genuine alkaloids of the plant (cf. Frederiksen & Stermitz, 1996). Swertiamarin (**6**) and gentiopic-roside (**7**) are iridoids that are particularly susceptible to this treatment since they provide a good yield of the stable pyridine alkaloid gentianine (**7e**). Most other iridoids give less stable alkaloids and usually in poorer yield. The question of whether gentianine and the other *Gentiana* alkaloids are artifacts or inherent in the living plant has been discussed at some length by Hegnauer (1966), but we have preferred only to register the presence of gentianine in Table 6.1, where we consider that a report of this compound merely indicates that **6** and/or **7** are present in a particular plant species.

Finally, we have suggested an alternative structure for the compound gentioflavoside (**7c**) in Fig. 6.7, since the one originally proposed (Popov &

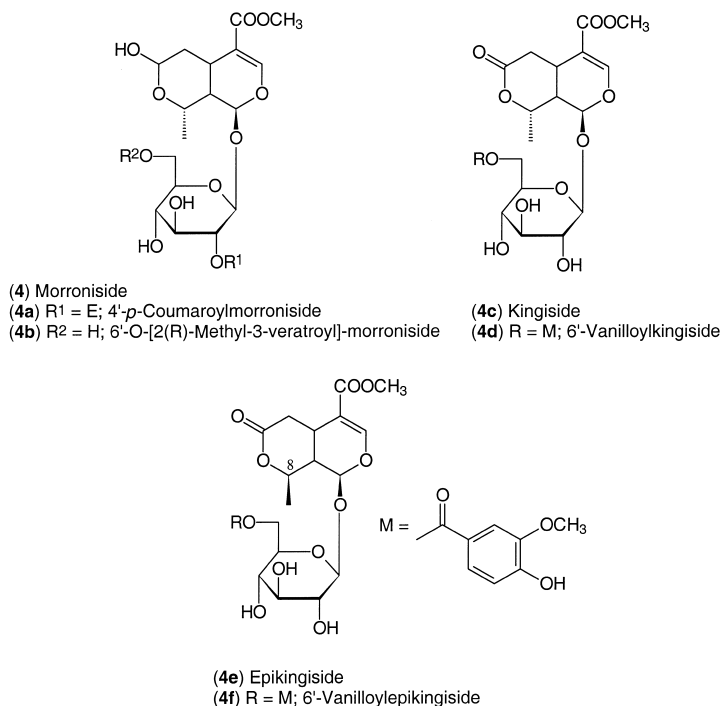
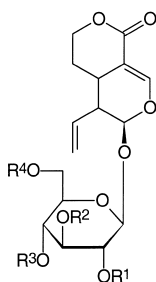


Figure 6.4. Secoiridoids of Gentianaceae: morroniside (4) and kingiside (4c) and their derivatives (see the acyl moieties E and H in Fig. 6.2).

Marekov, 1971b) would be chemically unstable and would have lost the sugar moiety during chromatographic isolation.

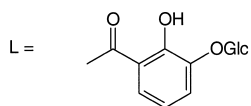
The known occurrences of iridoids in the Gentianaceae are listed in Table 6.1. These compounds apparently have been found, or at least detected, in all cases in which they have been sought. An example of this is the large survey performed by van der Sluis (1985) on five populations of *Blackstonia perfoliata* and 99 populations of 11 species of *Centaurium*. Iridoids were found in all taxa investigated.

It appears that the biosynthetic pathway leading from sweroside (5) to swertiamarin (6) and gentiopicroside (7) is universally present in Gentianaceae. At least one of these compounds or their derivatives is found in practically all species investigated for iridoids. It should be noted that 5 is a fairly common compound in Gentianales and Cornales, but 6 and 7 have much more limited distributions, so far being recorded elsewhere only in a few species of Dipsacaceae (Jensen *et al.*, 1975; Jensen, 1992).

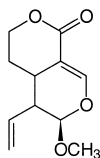
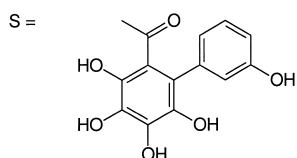
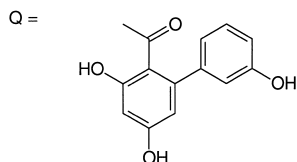
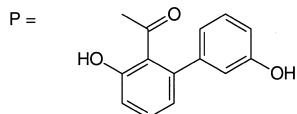


- (5) Sweroside
 (5a) R₁ = C; Deacetylcentapicrin
 (5b) R₁ = D; 2'-(2,3-Dihydroxybenzoyl)sweroside
 (5c) R₁ = P; Amaropanin
 (5d) R₁ = Q; Amarogentin
 (5e) R₂ = A; 3'-Acetylsweroside
 (5f) R₂ = C; Decentapicrin A
 (5g) R₂ = D; 3'-Sinapoylsweroside
 (5h) R₃ = C; Decentapicrin B
 (5i) R₄ = C; Decentapicrin C
 (5j) R₄ = Glc; Swertiapunimarin
 (5k) R₁ = C; R₂ = A; Centapicrin
 (5l) R₁ = R₂ = R₆ = A; R₃ = L; Trifloroside
 (5m) R₁ = O; R₂ = R₆ = A; R₃ = L; Scabraside
 (5n) R₁ = S; Amarogentin B

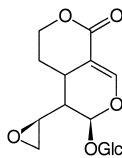
A = Acetyl
 B = *m*-Hydroxybenzoyl
 C = 2,3-Dihydroxybenzoyl
 D = Sinapoyl



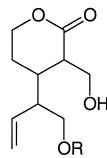
O = Benzoyl



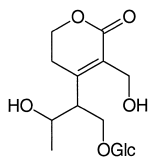
(5p) Anthocleistol



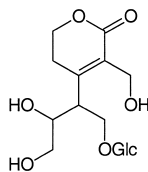
(5q) 5-Desoxyeustomoside



(5r) Amplexine
 (5s) R = Glc; Amplexine-1-glucoside



(5t) Potalioside I



(5u) Potalioside II

Figure 6.5. Secoiridoids of Gentianaceae: sweroside (5) and its derivatives.

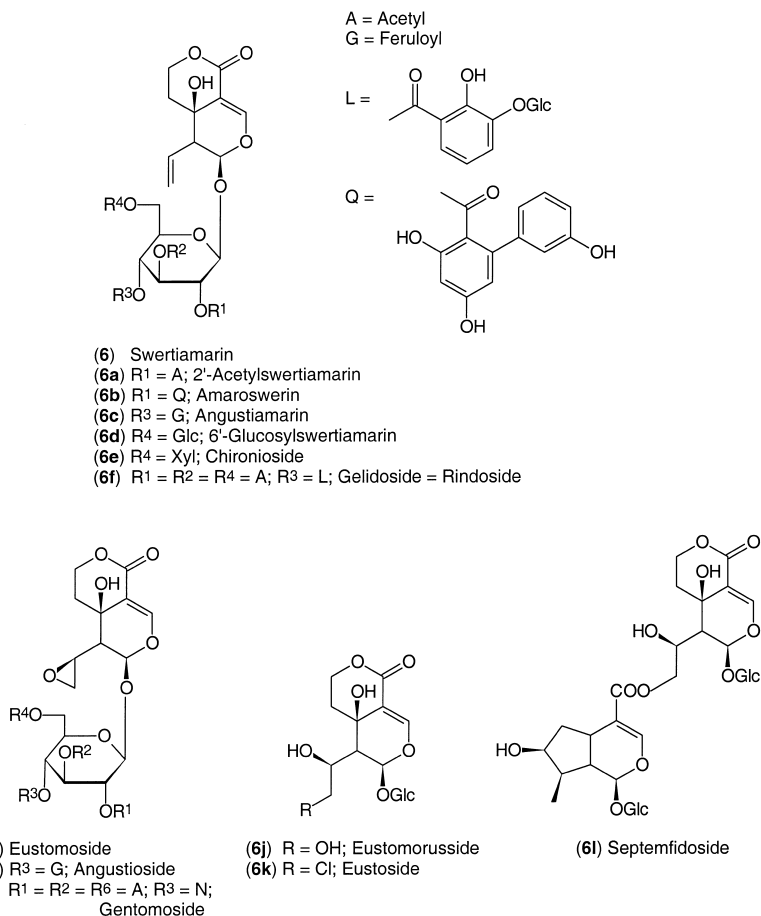


Figure 6.6. Secoiridoids of Gentianaceae: swertiamarin (6) and its derivatives.

XANTHONES

Xanthones (Figs. 6.8–6.9) have a rather restricted occurrence among higher plants, being found almost exclusively in Guttiferae and Gentianaceae (Carpenter *et al.*, 1969; Sultanbava, 1980; Mandal *et al.*, 1992a). Xanthones are sometimes found as the parent polyhydroxylated compounds but more often with a varying degree of substitution at the oxygen atoms. Most xanthones are mono- or poly-methyl ethers or are found as glycosides (Hostettmann & Wagner, 1977). Unlike iridoids, xanthones are apparently not present in all plant species investigated in the family Gentianaceae. This is documented by the systematic work of Hostettmann-Kaldas *et al.* (1981),

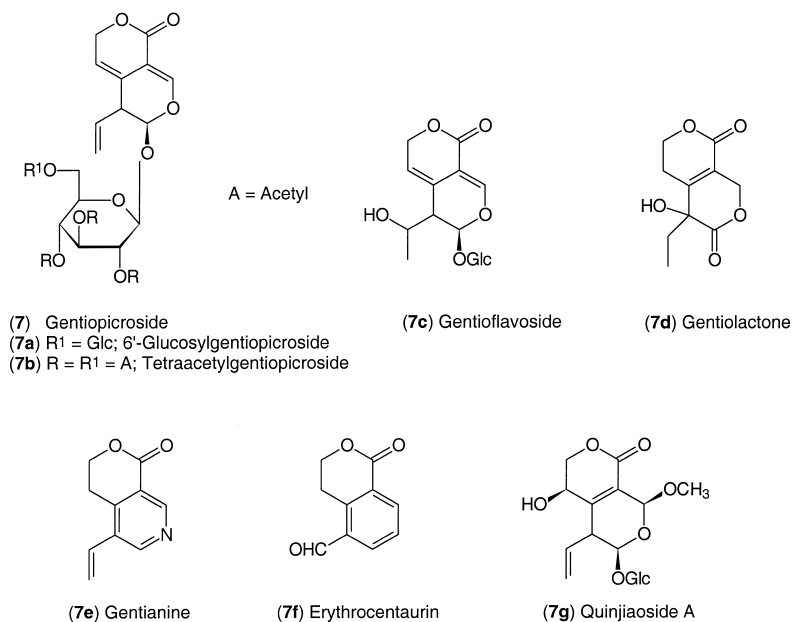


Figure 6.7. Secoiridoids of Gentianaceae; gentiopicroside (7) and its derivatives.

who found these compounds in only three out of six species of *Gentiana*, and van der Sluis (1985), who found that some species were apparently devoid of xanthenes, while others consistently contained them and others again were variable in xanthone content.

The widespread occurrence and variation in oxidation pattern has been used by some workers to compute cladograms for taxonomic analysis. In their approach, Rezende and Gottlieb (1973) and Gottlieb (1982) consider the xanthenes from Guttiferae (Clusiaceae) and Gentianaceae as a single entity with a common biosynthetic pathway to the compounds. From a frequency count, they come to the conclusion that the 1,3,5,6- and 1,3,6,7-tetraoxygenation patterns are the primitive state, and using these criteria they calculate scores for reduction and oxygenation in the A- and the B-ring. Thereby they assess the evolutionary advancement of six genera of Gentianaceae. This approach assumes (1) that the biosynthetic pathway is identical in Guttiferae and Gentianaceae, (2) that the "normal" xanthenes and the C-glucoxanthone mangiferin (10) have the same biosynthesis, and, as a consequence of this, (3) that reduction is an important feature in the formation of xanthenes in Gentianaceae. Below we will show that none of

Table 6.1. *The known occurrence of iridoids in Gentianaceae*

Species	Compounds reported ^a	References ^b
<i>Anthocleista amplexicaulis</i>	3j, 3k, 5r, 5s, 6	1, 2
<i>Anthocleista djalensis</i>	5, 5r	3
<i>Anthocleista grandiflora</i>	3j, 3k	4
<i>Anthocleista liebrechtsiana</i>	6	5
<i>Anthocleista nobilis</i>	5p	6
<i>Anthocleista procera</i>	6, 7e	7
<i>Anthocleista vogelii</i>	3, 3a, 5	4, 8
<i>Anthocleista zambeiaca</i>	5, 7f	9
<i>Blackstonia perfoliata</i>	5, 6, 7	10
<i>Centaurium chilense</i>	5	11
<i>Centaurium chloodes</i>	5f, 6	11
<i>Centaurium erythraea</i> (= <i>Erythraea centaurium</i>)	2l, 2v, 3d, 3f, 5, 5a, 5k, 6, 7, 7c, 7e	12–17
<i>Centaurium linarifolium</i>	5f, 7f	18
<i>Centaurium littorale</i>	5a, 5f, 5h, 5i, 5k	13
<i>Centaurium majus</i>	5h, 6	11
<i>Centaurium maritimum</i>	5, 6, 7	11
<i>Centaurium pulchellum</i>	5, 6, 7	11
<i>Centaurium quitense</i>	5, 6, 7	11
<i>Centaurium scilloides</i>	5f, 6	11
<i>Centaurium spicatum</i>	5, 6, 7	11
<i>Centaurium tenuiflorum</i>	5, 6, 7	11
<i>Chelonanthus chelonoides</i> (= <i>C. alatus</i>)	3b, 3c, 5	19
<i>Chironia baccifera</i>	5, 6, 6e, 6g, 7	20
<i>Chironia krebsii</i>	5, 6, 6e, 6g, 7	20
<i>Chironia palustris</i>	5, 6, 6g, 6j, 7	20
<i>Chironia purpurascens</i>	5, 6, 6e, 6g, 6j, 7	20
<i>Cicendia filiformis</i>	7	21
<i>Coutoubea spicata</i>	6, 7	22
<i>Curtia tenuifolia</i>	2d, 3a, 3d, 3g, 5, 6, 7	23
<i>Enicostema hyssopifolium</i>	7f	24
<i>Eustoma russellianum</i>	5, 6, 6g, 6j, 6k, 7	25
<i>Exacum affine</i>	2e, 7	26
<i>Exacum quinquenervium</i>	7e	27
<i>Exacum tetragonum</i>	3k, 7	28
<i>Fagraea fragrans</i>	7e	29
<i>Fagraea gracilipes</i>	5, 5g	30
<i>Fagraea obovata</i>	5, 7	31
<i>Faroa chalcophila</i>	7	32
<i>Faroa graveolens</i>	7	33
<i>Gentiana affinis</i>	7	34
<i>Gentiana algida</i>	5, 5b, 5l, 5s, 6f, 7	35
<i>Gentiana alpina</i>	5, 6, 6d, 6g, 6j	36

Table 6.1. (*cont.*)

Species	Compounds reported ^a	References ^b
<i>Gentiana asclepiadea</i>	7c, 7e	37, 38
<i>Gentiana atuntsiensis</i>	7	39
<i>Gentiana bulgarica</i>	7	40
<i>Gentiana burseri</i>	5d, 7	41
<i>Gentiana calycosa</i>	7	34
<i>Gentiana campestris</i>	5q, 6, 6g, 6j, 6k, 7	42
<i>Gentiana caucasica</i>	7a	43
<i>Gentiana cephalantha</i>	7	39
<i>Gentiana cephantha</i>	7	44
<i>Gentiana cerastioides</i>	7	34
<i>Gentiana depressa</i>	2c, 2s, 3m, 3n, 3o	45–47
<i>Gentiana detonsa</i>	7	34
<i>Gentiana farreri</i>	5, 6, 7	48
<i>Gentiana formosana</i>	5, 5e	49
<i>Gentiana gelida</i>	5l, 6, 6f, 6g, 6i, 6j, 7	50
<i>Gentiana kaufmanniana</i>	7e	51
<i>Gentiana kurroo</i>	4, 7	52 (and see text)
<i>Gentiana lactea</i>	2, 5, 5a, 6, 7	55
<i>Gentiana lutea</i>	4, 5, 5d, 6, 7	52, 56
<i>Gentiana macrophylla</i>	5, 6, 7, 7g	57, 58
<i>Gentiana manshurica</i>	7	59
<i>Gentiana olgae</i>	7e	60
<i>Gentiana olivieri</i>	7e	61
<i>Gentiana pannonica</i>	5c	62
<i>Gentiana pedicellata</i>	2, 2b, 2c, 2e, 2f, 2g, 2h	63, 64
<i>Gentiana punctata</i>	2u, 5, 6, 7, 7c	21
<i>Gentiana purpurea</i>	5c, 5d, 6b, 7, 7d	65, 66
<i>Gentiana pyrenaica</i>	2, 2m, 4, 4a, 4b, 4c, 4d, 4e, 4f	67–70
<i>Gentiana regescens</i>	7e	71
<i>Gentiana rhodantha</i>	3q, 4c, 4e, 5, 6	72
<i>Gentiana rigescens</i>	7	39
<i>Gentiana scabra</i>	2, 5m, 6, 6f, 7, 7b	44, 73, 74
<i>Gentiana septemfida</i>	2, 5, 6, 6f, 6g, 6j, 6k, 6l, 7	75
<i>Gentiana sino-ornata</i>	5, 6, 7	48
<i>Gentiana strictiflora</i>	7	34
<i>Gentiana suffrutescens</i>	7	39
<i>Gentiana thunbergii</i>	4	76
<i>Gentiana tianscanica</i>	7e	60
<i>Gentiana tibetica</i>	7	77
<i>Gentiana triflora</i>	5l, 6, 7	78
<i>Gentiana uchiyamana</i>	6, 7	79
<i>Gentiana urnula</i>	2a, 2n, 3n, 3o, 3p	80
<i>Gentiana verna</i>	2, 2j, 2k, 3d, 3e, 3g, 3h, 3i, 5	81–83
<i>Gentiana vvedenskyi</i>	7e	60
<i>Gentianella azurea</i>	2, 6, 7	77
<i>Gentianella bulgarica</i>	2u, 5, 6, 6g, 7	21

Table 6.1. (cont.)

Species	Compounds reported ^a	References ^b
<i>Halenia campanulata</i>	3a	84
<i>Halenia corniculata</i>	3a, 5, 6	85
<i>Halenia elliptica</i>	5, 6	86
<i>Ixanthus viscosus</i>	2, 6, 7	87
<i>Lisianthus jefensis</i>	3r	88
<i>Lisianthus seemanii</i>	3r	16
<i>Lomatogonium carinthiacum</i>	6	89
<i>Potalia amara</i>	5t, 6	90
<i>Potalia</i> sp.	5u, 6	90
<i>Sabatia angularis</i>	7	91
<i>Sabatia elliotii</i>	5d, 7e	21, 91
<i>Schultesia guianensis</i>	6, 7e	92, 93
<i>Swertia alata</i>	6	94
<i>Swertia angustifolia</i>	5, 6, 6c, 6g, 6h	95
<i>Swertia arisanensis</i>	5	96
<i>Swertia bimaculata</i>	5, 6, 7	86
<i>Swertia calycina</i>	5, 7	97
<i>Swertia caroliniensis</i>	2c, 7	98
<i>Swertia chirata</i>	5, 6b	99
<i>Swertia cincta</i>	5, 6, 7	86
<i>Swertia connata</i>	7e	60
<i>Swertia davidi</i>	7e	100
<i>Swertia elongata</i>	5a, 6	101
<i>Swertia erythrostricta</i>	5, 6, 7	86
<i>Swertia fasciculata</i>	5, 6, 7	86
<i>Swertia graciliflora</i>	7e	102
<i>Swertia japonica</i>	2p, 2q, 2r, 5, 5d, 6, 6b, 7	103–106
<i>Swertia lawii</i>	7f	24
<i>Swertia macrosperma</i>	6, 7	86
<i>Swertia marginata</i>	7e	102
<i>Swertia mileensis</i>	5, 6, 6a	107, 108
<i>Swertia mussotii</i>	5d	109
<i>Swertia nervosa</i>	3a, 5, 6	110
<i>Swertia patens</i>	6	111
<i>Swertia petiolata</i>	7	112
<i>Swertia pseudochinensis</i>	6	113
<i>Swertia pubescens</i>	5, 6, 7	86
<i>Swertia punicea</i>	5, 5b, 6, 6d, 7, 7g	114, 115
<i>Swertia randaiensis</i>	7e	116
<i>Swertia tetrapetala</i>	6	117

Notes:

^a Bold numbers refer to the compounds in Figs. 6.2–6.7.^b References: 1: Weber, 1974. 2: Rasoanaivo *et al.*, 1994. 3: Onocha *et al.*, 1995. 4: Chapelle, 1976a. 5: Cornelis & Chapelle, 1976. 6: Madubunyi *et al.*, 1994. 7: Koch, 1965. 8: Chapelle,

1974. 9: Chapelle, 1976b. 10: Chapelle, 1973. 11: van der Sluis, 1985. 12: van der Sluis *et al.*, 1983. 13: van der Sluis & Labadie, 1981a. 14: Do *et al.*, 1987. 15: Rulko & Witkiewicz, 1972. 16: Sakina & Aota, 1976. 17: Tagaki *et al.*, 1982. 18: van der Sluis & Labadie, 1981b. 19: Shiobara *et al.*, 1994. 20: Wolfender *et al.*, 1993. 21: Hegnauer, 1966. 22: Schaufelberger *et al.*, 1987. 23: Kuwajima *et al.*, 1996a. 24: Ghosal *et al.*, 1974c. 25: Uesato *et al.*, 1979. 26: Kuwajima *et al.*, 1996b. 27: Delaude, 1984. 28: Das *et al.*, 1984. 29: Wan *et al.*, 1972. 30: Cambie *et al.*, 1990. 31: Jensen, 1992. 32: Delaude, 1985. 33: Delaude & Darimont, 1985. 34: Hostettmann-Kaldas *et al.*, 1981. 35: Tan *et al.*, 1996. 36: Mpondo *et al.*, 1990a. 37: Rulko & Nadler, 1970. 38: Mpondo & Chulia, 1988. 39: Luo & Lou, 1986. 40: Thanh *et al.*, 1987. 41: Stefanou *et al.*, 1976. 42: Mpondo *et al.*, 1990b. 43: Topuriya, 1978. 44: Yang *et al.*, 1985. 45: Chulia & Kaouadji, 1985. 46: Chulia *et al.*, 1994. 47: Chulia *et al.*, 1996. 48: Schaufelberger & Hostettmann, 1987. 49: Chung & Lin, 1993. 50: Calis *et al.*, 1990. 51: Sadykov, 1987. 52: Inouye & Nakamura, 1971b. 53: Sarg *et al.*, 1990. 54: Sarg *et al.*, 1991. 55: Schaufelberger & Hostettmann, 1988. 56: Bricout, 1974. 57: Wang & Lou, 1988. 58: Liu *et al.*, 1994a. 59: Zhang *et al.*, 1993. 60: Rakhmatullaev, 1971. 61: Rakhmatullaev *et al.*, 1969a. 62: Wagner & Vasirian, 1974. 63: Garcia & Chulia, 1987. 64: Chulia *et al.*, 1986. 65: Nyireddy *et al.*, 1986. 66: Suhr *et al.*, 1978. 67: Garcia *et al.*, 1989a. 68: Garcia *et al.*, 1989b. 69: Garcia *et al.*, 1989c. 70: Garcia *et al.*, 1990. 71: Sun & Xia, 1984. 72: Ma *et al.*, 1994. 73: Ikeshiro & Tomita, 1983. 74: Ikeshiro *et al.*, 1990. 75: Calis *et al.*, 1992. 76: Takeda & Inouye, 1976. 77: Zhang & Yang, 1994. 78: Inouye *et al.*, 1974b. 79: Chung & Lee, 1982. 80: Liu *et al.*, 1994b. 81: Mpondo *et al.*, 1989. 82: Mpondo & Garcia, 1990a. 83: Mpondo & Garcia, 1990b. 84: Recio-Iglesias *et al.*, 1992. 85: Rodriguez *et al.*, 1995b. 86: Gao *et al.*, 1994. 87: Ortega *et al.*, 1988. 88: Hamburger *et al.*, 1990. 89: Schaufelberger & Hostettmann, 1984. 90: S. R. Jensen & J. Schripsema, unpubl. 91: Korte, 1955. 92: Nobrega & Craveiro, 1988. 93: Terreaux *et al.*, 1995. 94: Khan *et al.*, 1979. 95: Luo & Nie, 1992. 96: Lin *et al.*, 1987. 97: Rodriguez *et al.*, 1995a. 98: Coscia *et al.*, 1969. 99: Chaudhuri & Daniewski, 1995. 100: Guo & Chen, 1980. 101: Kong *et al.*, 1995. 102: Rakhmatullaev *et al.*, 1969b. 103: Inouye *et al.*, 1971b. 104: Ikeshiro & Tomita, 1984. 105: Ikeshiro & Tomita, 1985. 106: Ikeshiro & Tomita, 1987. 107: Kikuzaki *et al.*, 1996. 108: He & Nie, 1980. 109: Sun *et al.*, 1991. 110: Luo & Nie, 1993a. 111: Liang *et al.*, 1984. 112: Gröger & Simchen, 1969. 113: Kitamura *et al.*, 1988. 114: Luo & Nie, 1993b. 115: Tan *et al.*, 1993. 116: Wu *et al.*, 1976. 117: Agata *et al.*, 1981.

these assumptions appears to be valid. Massias *et al.* (1982) carried out an analysis of four genera of Gentianaceae using the oxygenation patterns of the xanthenes and the presence of some sugars and some C-glucoflavones to construct a phyletic scheme. In this scheme *Gentiana* comes out on one branch while *Comastoma*, *Gentianella*, and *Gentianopsis* appear on another. In that work it is assumed that the trisubstituted xanthenes represent the primitive state, while the higher the oxidation state of the compounds, the more advanced the taxon. We agree with this assumption. Mészáros (1994) discusses the above two works and makes some unconventional evolutionary assumptions based on both the positions and the number of oxidations in the xanthone nuclei. He calculates advancement indices for 13 taxa, which are compared with those calculated on the basis of the other workers' hypotheses. One problem inherent in Mészáros's calculations is

the use of an “outgroup”, namely *Anthocleista*, which was considered a member of Loganiaceae (Struwe *et al.*, 2002 (Chapter 2, this volume)). In the present work, this taxon is a true member of Gentianaceae. Another problem is that there appears to be more than one line of xanthone advancement in the family (see below).

Biosynthesis

Biosynthetically, the xanthones are of mixed shikimate and acetate origin (Fig. 6.8). Thus phenylalanine, which is formed from shikimate, loses two carbon atoms from the side-chain and is oxidized to form *m*-hydroxybenzoic acid. This combines with three units of acetate (probably via malonate) to produce the intermediate shown. Proper folding and ring-closure gives a substituted benzophenone, which by an oxidative phenol coupling generates the central ring of the xanthone moiety.

Note that this oxidative coupling can in principle take place in two ways (see Fig. 6.8), depending on the folding of the benzophenone: either in *ortho*- or in *para*-position to the hydroxyl substituent in the potential B-ring to give 1,3,5-trihydroxyxanthone (**8**) or the 1,3,7-substituted analogue gentisein (**9**), respectively. Thus, depending on the orientation of the intermediate, two different hydroxylation patterns can be found. This will be discussed below.

Experimental proof for the overall pathway has been obtained from experiments performed on *Gentiana lutea* (Atkinson *et al.*, 1968; Gupta & Lewis, 1971): when plants were fed ¹⁴C-labeled phenylalanine, the label was recovered solely in the B-ring (Fig. 6.8). Conversely, feeding of ¹⁴C-labeled acetate gave incorporation of which the main part was found in the A-ring. Finally, administration of a ³H-labeled analogue of the shown 2,3',4,6-tetrahydroxybenzophenone proved that this was also a precursor and a likely intermediate. In the feeding experiments the compounds isolated from the plants were the monomethyl derivatives gentisin and isogentisin, obtained as a mixture and degraded to gentisein (**9**) in which the incorporation was measured. The alternative ring-closure to **8** has recently been shown to take place in cultured cells of *Centaurium erythraea*, where 2,3',4,6-tetrahydroxybenzophenone is the precursor for 1,3,5-trihydroxyxanthone (**8**; Fig. 6.8) (Peters *et al.*, 1998). Furthermore, in these cell cultures compound **8** is selectively oxidized by a xanthone 6-hydroxylase to 1,3,5,6-tetrahydroxyxanthone (Schmidt *et al.*, 2000).

Interestingly, the iridoids amarogentin (**5d**) and amaroswerin (**6b**), first isolated from *Swertia japonica* (Inouye & Nakamura, 1971a), both contain

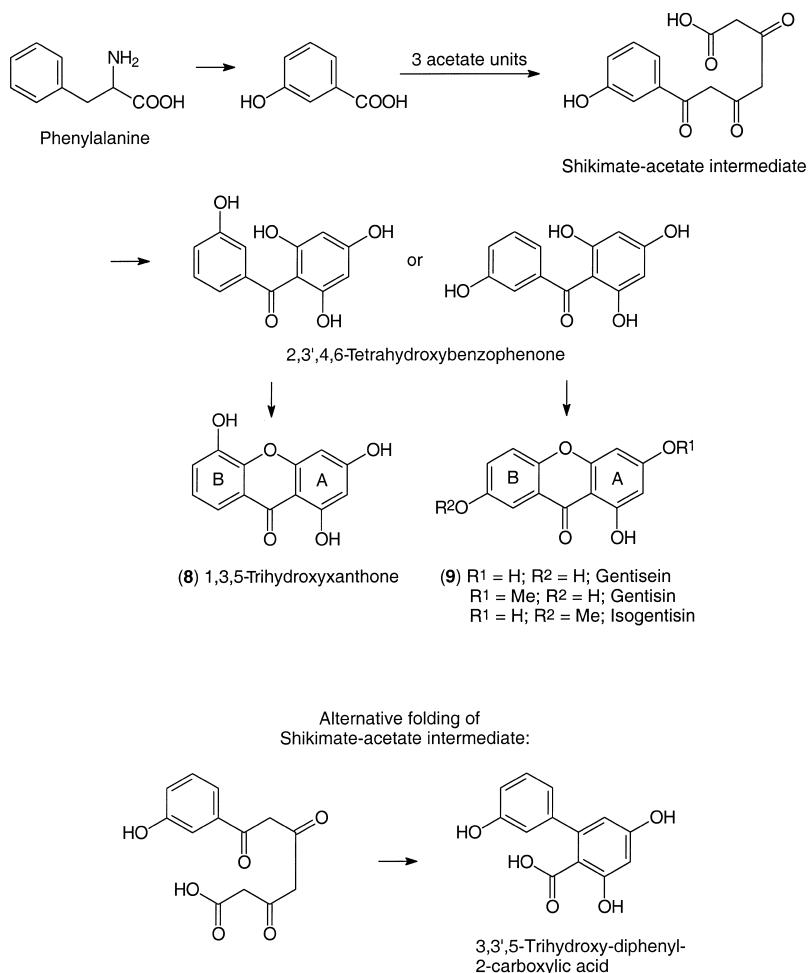


Figure 6.8. Biosynthetic pathways leading to the parent xanthenes **8** and **9**, and to the *Swertia* acid.

the unique 3,3',5-trihydroxydiphenyl-2-carboxylic acid moiety. The authors noted the similarity between the oxidation pattern of this acyl moiety and the above xanthenes gentisin and isogentisin, which are common in Gentianaceae, and they suggested that they had a common biogenetic precursor, namely the shikimate–acetate intermediate discussed above (Fig. 6.8). The alternative folding pattern shown would, by ring-closure, produce the substituted diphenyl-2-carboxylic acid. Actual work on this idea was published only relatively recently by Inouye's group (Kuwajima *et al.*,

1990). Administration of radiolabeled acetate, phenylalanine, and benzoic acid to *Swertia japonica* showed that all were precursors and that the above hypothesis is very likely to be true.

Results

We have recorded approximately 600 occurrences of about 100 different xanthenes in 110 species and 21 genera in the family (Table 6.2). Some plants are either very rich in these compounds or have been heavily worked on; an example is *Canscora decussata*, from which 31 different compounds have been isolated. In order to simplify the presentation of this large amount of data, we have preferred to demonstrate only the oxidation patterns of the parent xanthenes, ignoring the variation in O-substitution with methyl, glycosyl, and other groups. This left 21 oxidation patterns (**8a–8n** and **9a–9n**) which could be presented in a presumed biosynthetic double tree- (or rather shrub-)like structure (Fig. 6.9). In the following discussion a number in bold will therefore represent not a single compound, but rather a group of compounds with the same oxidation pattern.

As discussed above, the biosynthetic pathway has been demonstrated in cultured cells of *Centaurium erythraea* for the formation of 1,3,5-trihydroxy-xanthone (**8**), and alternatively, in *Gentiana lutea*, of 1,3,7-substituted genti-sein (**9**). This should be sufficient evidence for the fact that **8** and **9** are actually the parent xanthenes, and that these are not formed by reduction of tetrasubstituted precursors (**8j** and **9j**) in the plants, as presumed by Rezende and Gottlieb (1973). Also, no dioxygenated compounds have yet been discovered from the Gentianaceae. If reduction to less substituted compounds had been a valid mechanism in the biosynthetic pathway, we find it likely that at least a few representatives arising from this would have been found, particularly considering that such a large number of compounds are now known.

Almost all the compounds **9a–9n** may comfortably be derived from **9** by one or more (enzymatic) oxidations in positions *ortho* or *para* to an existing phenolic hydroxyl group (the oxidized positions in each case are indicated by the number above the arrow leading to the more oxidized compound in Fig. 6.9). The only position in **9** (or **9c**) which is not activated for enzymatic oxidation by one or more *ortho*- or *para*-hydroxyl groups is the C-5 carbon in the B-ring. This argument is supported by the fact that out of the 280 compounds in this part of the tree only eight (represented by **9e** and **9d**) have been formed by oxidation at C-5. Only after introduction of an oxygen at C-6 or C-8 is oxidation at C-5 likely. The remaining compounds may now easily be derived from a less oxidized compound

Table 6.2. *The known occurrence of xanthenes in Gentianaceae*

Taxon	Compounds reported ^a	References ^b
<i>Anthocleista vogelii</i>	9j (3)	1, 2
<i>Blackstonia perfoliata</i>	9j (1)	3
<i>Canscora decussata</i>	8 (5), 8f (6), 8g (12), 8h (3), 9f (1), 9j (4), 9n (4)	4–12
<i>Centaurium cachanlahuen</i>	8h (1), 8j (1), 9j (2)	13
<i>Centaurium erythraea</i>	8f (1), 8g (1), 8h (1), 8j (1), 8n (1), 9j (1)	14
<i>Centaurium linarifolium</i>	8f (2), 8h (4), 8n (1), 9j (2)	15–17
<i>Centaurium littorale</i>	8h (2), 8j (2)	18
<i>Centaurium pulchellum</i>	8j (1), 9j (2)	19
<i>Centaurium scilloides</i>	8h (2), 8j (2)	19
<i>Chironia krebsii</i>	8 (6), 8f (1), 8h (5), 9 (1), 9j (4)	20
<i>Comastoma pulmonarium</i>	8j (2), 9j (4)	21
<i>Eustoma grandiflorum</i>	8 (1), 8g (1), 8h (1), 9 (1), 9j (1)	22
<i>Frasera albicaulis</i>	8 (1), 8a (1), 8b (1), 8c (1), 8j (1), 9 (2), 9a (2), 9b (2), 9c (2)	23
<i>Frasera albomarginata</i>	8 (1), 8a (1), 8c (1), 8j (1), 9 (1), 9b (1), 9c (1)	24
<i>Frasera caroliniensis</i>	8a (1), 8b (1), 8c (1), 8j (1), 9a (1), 9c (1)	25
<i>Frasera speciosa</i>	8a (1), 8b (1), 8c (1), 9a (1), 9c (2)	24
<i>Frasera tetrapetala</i>	8c (1), 9c (1)	26
<i>Gentiana acaulis</i>	9j (2)	27
<i>Gentiana algida</i>	8j (2), 8l (1)	28
<i>Gentiana asclepiadea</i>	9 (1)	29, 30
<i>Gentiana barbata</i>	9j (8)	31–34
<i>Gentiana bavarica</i>	9j (10)	35–37
<i>Gentiana brachyphylla</i>	9j (3)	38
<i>Gentiana campestris</i>	8j (5), 8l (2)	39–41
<i>Gentiana cerastioides</i>	8j (4)	42
<i>Gentiana ciliata</i>	9 (4), 9j (18)	43, 44
<i>Gentiana corymbifera</i>	8j (5), 8l (3)	45
<i>Gentiana corymbosa</i>	8j (4)	46
<i>Gentiana dasyantha</i>	8j (4)	46
<i>Gentiana detonsa</i>	9j (4)	42
<i>Gentiana favrati</i>	9j (3)	38
<i>Gentiana karelinii</i>	8j (1), 9j (4)	29
<i>Gentiana kochiana</i>	9j (6)	47, 48
<i>Gentiana lactea</i>	8j (5)	49
<i>Gentiana lutea</i>	9 (7), 9a (1), 9j (1)	50–55
<i>Gentiana marcaillhouana</i>	8j (1), 9 (1)	56
<i>Gentiana nivalis</i>	9j (3)	38
<i>Gentiana orbicularis</i>	9j (3)	57
<i>Gentiana pannonica</i>	9 (1)	53
<i>Gentiana punctata</i>	9 (1)	53

Table 6.2. (cont.)

Taxon	Compounds reported ^a	References ^b
<i>Gentiana purpurea</i>	9 (1)	53
<i>Gentiana rostani</i>	9j (3)	38
<i>Gentiana schleicheri</i>	9j (2)	38
<i>Gentiana strictiflora</i>	8j (4)	42
<i>Gentiana utriculosa</i>	9j (2)	38
<i>Gentiana verna</i>	8j (1), 9j (8)	38, 58, 59
<i>Gentianella azurea</i>	8j (1)	60
<i>Gentianella bellidifolia</i>	8j (5), 8l (1), 9l (1)	61
<i>Gentianella campestris</i>	8j (5), 8l (2), 9j (1)	61
<i>Gentianella germanica</i>	8j (4), 8l (2)	61, 62
<i>Gentianella ramosa</i>	8j (5), 8l (2), 9j (1)	61, 62
<i>Gentianella serotina</i>	9l (3)	57
<i>Gentianella stenocalyx</i>	9 (1), 9j (5)	57
<i>Gentianella tenella</i>	8j (1), 9j (2)	61
<i>Gentianopsis</i> (12 species)	9 (2), 9j (5)	57
<i>Halenia asclepiadea</i>	8a (1), 8c (1), 9c (1)	46, 63
<i>Halenia campanulata</i>	8a (2), 8c (1)	64
<i>Halenia corniculata</i>	9a (2), 9c (2), 9d (5)	65
<i>Halenia elliptica</i>	8a (1), 8c (1), 8j (1), 9a (1), 9d (1)	66, 67
<i>Hoppea dichotoma</i>	8 (2), 8f (4), 8g (2)	68
<i>Hoppea fastigiata</i>	9e (2), 9j (1)	69–72
<i>Ixanthus viscosus</i>	9n (2)	73
<i>Lomatogonium carinthiacum</i>	8j (2), 9 (1), 9j (2)	74
<i>Lomatogonium rotatum</i>	8j (1), 9j (1)	75
<i>Macrocarpaea glabra</i>	9 (1), 9j (1)	76
<i>Orphium frutescens</i>	9j (3)	77
<i>Schultesia lisianthioides</i> (= <i>Xestaea lisianthioides</i>)	8 (2), 8a (2), 8f (1), 8j (1), 9j (3)	78
<i>Swertia alata</i>	8j (1)	79
<i>Swertia angustifolia</i>	8b (1), 8j (4), 8l (2), 9 (1), 9c (1), 9j (6), 9l (2)	80, 81
<i>Swertia bimaculata</i>	8b (3), 8c (1), 8d (1), 8j (3), 9c (3)	82, 83
<i>Swertia calycina</i>	8 (1), 9j (3)	65
<i>Swertia chirata</i>	8j (4), 9j (5)	84–86
<i>Swertia chirayita</i>	8j (2), 9j (1)	87, 88
<i>Swertia connata</i>	8j (1), 9j (3)	89, 90
<i>Swertia cordata</i>	9m (2)	91, 92
<i>Swertia decussata</i>	9j (1)	47
<i>Swertia devidi</i>	8j (1)	93
<i>Swertia dilatata</i>	9j (1)	94
<i>Swertia elongata</i>	8j (2)	95
<i>Swertia erythrosticta</i>	8j (6), 9j (3)	96
<i>Swertia fasciculata</i>	8j (1)	66

Table 6.2. (cont.)

Taxon	Compounds reported ^a	References ^b
<i>Swertia franchetiana</i>	8 (1), 8j (1)	97
<i>Swertia gracilescens</i>	9j (1)	94
<i>Swertia hookeri</i>	8 (2), 8j (7), 9j (2)	98
<i>Swertia iberica</i>	8j (1), 9j (6), 9k (1)	35, 99, 100
<i>Swertia japonica</i>	8j (7), 9 (1), 9j (3)	101–105
<i>Swertia lawii</i>	8j (2), 9j (4), 9l (1)	106
<i>Swertia macrosperma</i>	8j (3)	107
<i>Swertia mileensis</i>	8a (1), 8c (1)	108, 109
<i>Swertia mussotii</i>	8 (1), 8j (5), 9j (6), 9l (1)	110–112
<i>Swertia nervosa</i>	9j (4)	94
<i>Swertia paniculata</i>	8j (5), 9j (7), 9l (1)	113, 114
<i>Swertia patens</i>	8 (1), 8j (1), 9j (2)	115
<i>Swertia perennis</i>	8j (2), 9j (7)	47, 59, 116, 117
<i>Swertia perfoliata</i>	8j (1), 9j (1)	118
<i>Swertia petiolata</i>	8j (3), 9 (2), 9j (2)	119–121
<i>Swertia przewalskii</i>	9j (7)	122
<i>Swertia punicea</i>	8j (1), 9j (3), 9m (1)	123, 124
<i>Swertia purpurascens</i>	8j (6), 9j (2), 9l (1), 9m (1)	125–127
<i>Swertia racemosa</i>	8j (3), 9j (3)	94
<i>Swertia randaiensis</i>	8j (2)	128, 129
<i>Swertia speciosa</i>	8j (4), 9 (3), 9j (4)	130–132
<i>Swertia swertopsis</i>	8j (1), 9j (3)	129
<i>Swertia tetrapetala</i>	8a (1), 8j (1), 9c (1)	133
<i>Swertia tetraptera</i>	8a (1), 9b (1)	134
<i>Swertia tosaensis</i>	8j (1)	125
<i>Swertia verticillifolia</i>	8j (4), 9j (2)	135
<i>Tripterospermum lanceolatum</i>	8f (1), 9b (1), 9f (1), 9l (3)	136–138
<i>Tripterospermum taiwanense</i>	9b (1), 9f (1)	139, 140
<i>Veratrilla baillonii</i>	8a (1), 8c (1), 9a (2), 9b (2), 9c (3)	141–143

Notes:

^a Bold numbers refer to the compounds in Fig. 6.9 (number of different compounds found in parentheses)

^b References: 1: Okorie, 1976. 2: Chapelle, 1974. 3: van der Sluis, 1985. 4: Ghosal *et al.*, 1976. 5: Ghosal & Chaudhuri, 1975. 6: Ghosal & Chaudhuri, 1973. 7: Ghosal *et al.*, 1973a. 8: Ghosal *et al.*, 1974a. 9: Ghosal *et al.*, 1977. 10: Ghosal & Biswas, 1979. 11: Ghosal *et al.*, 1971. 12: Chaudhuri & Ghosal, 1971. 13: Versluys *et al.*, 1982. 14: Kaoudaji *et al.*, 1986. 15: Parra *et al.*, 1985. 16: Parra *et al.*, 1984a. 17: Parra *et al.*, 1984b. 18: van der Sluis & Labadie, 1985. 19: Miana & Al-Hazimi, 1984. 20: Wolfender *et al.*, 1993. 21: Fan *et al.*, 1988. 22: Sullivan *et al.*, 1977. 23: Stout *et al.*, 1969a. 24: Dreyer & Bourell, 1981. 25: Stout & Balkenhol, 1969. 26: Agata *et al.*, 1984. 27: Plouvier *et al.*, 1967. 28: Butayarov *et al.*, 1993b. 29: Kitanov *et al.*, 1991. 30: Goetz & Jacot-Guillarmod, 1977. 31: Pureb *et al.*, 1991. 32: Nikolaeva *et al.*, 1980a. 33: Nikolaeva *et al.*, 1980b. 34: Nikolaeva *et al.*, 1981. 35: Denisova *et al.*, 1980b. 36: Hostettmann *et al.*, 1974. 37: Hostettmann *et al.*, 1976. 38: Hostettmann & Jacot-Guillarmod, 1977. 39: Kaldas *et al.*, 1974. 40: Kaldas *et al.*, 1975. (cont.)

Note b of Table 6.2 (*cont.*)

41: Kaldas *et al.*, 1978. 42: Hostettmann-Kaldas *et al.*, 1981. 43: Massias *et al.*, 1976. 44: Goetz *et al.*, 1978. 45: Massias *et al.*, 1981. 46: Recio *et al.*, 1990. 47: Rivaille *et al.*, 1969. 48: Guyot *et al.*, 1968. 49: Schaufelberger & Hostettmann, 1988. 50: Hayashi & Yamagishi, 1988. 51: Lubsandorzheva *et al.*, 1986. 52: Nikolaeva *et al.*, 1983. 53: Verney & Debelmas, 1973. 54: Bellmann & Jacot-Guillarmod, 1973. 55: Atkinson *et al.*, 1969. 56: Luong *et al.*, 1980. 57: Massias *et al.*, 1982. 58: Hostettmann & Jacot-Guillarmod, 1974. 59: Rivaille & Raulais, 1969. 60: Zhang & Yang, 1994. 61: Carbonnier *et al.*, 1977. 62: Hostettmann-Kaldas & Jacot-Guillarmod, 1978. 63: Stout & Fries, 1970. 64: Recio-Iglesias *et al.*, 1992. 65: Rodriguez *et al.*, 1995b. 66: Gao *et al.*, 1994. 67: Sun *et al.*, 1983. 68: Ghosal *et al.*, 1978a. 69: Mukherjee *et al.*, 1995. 70: Mukherjee *et al.*, 1990. 71: Mukherjee *et al.*, 1991a. 72: Mukherjee *et al.*, 1991b. 73: Ortega *et al.*, 1988. 74: Sorig *et al.*, 1977. 75: Khishgee & Pureb, 1993. 76: Stout *et al.*, 1969b. 77: Roitman *et al.*, 1992. 78: Terreaux *et al.*, 1995. 79: Khan *et al.*, 1979. 80: Dhoubhadel *et al.*, 1980. 81: Ghosal *et al.*, 1978b. 82: Inouye *et al.*, 1971c. 83: Ghosal *et al.*, 1975b. 84: Ghosal *et al.*, 1973b. 85: Purushothaman *et al.*, 1973. 86: Mandal & Chatterjee, 1987. 87: Saxena & Mukherjee, 1992. 88: Asthana *et al.*, 1991. 89: Solov'eva *et al.*, 1980a. 90: Solov'eva *et al.*, 1980b. 91: Atta-ur-Rahman *et al.*, 1994. 92: Khan & Haqqani, 1981. 93: Yu, 1984. 94: Tomimori *et al.*, 1974. 95: Kong *et al.*, 1995. 96: Hu *et al.*, 1992. 97: Ding *et al.*, 1988. 98: Ghosal *et al.*, 1980. 99: Denisova *et al.*, 1980a. 100: Denisova *et al.*, 1980c. 101: Ashida *et al.*, 1994. 102: Ishimaru *et al.*, 1990. 103: Kanamori *et al.*, 1984. 104: Sakamoto *et al.*, 1982. 105: Basnet *et al.*, 1994. 106: Ghosal *et al.*, 1975a. 107: Zhou & Liu, 1990. 108: Liu & Huang, 1982. 109: He *et al.*, 1982. 110: Sun & Ding, 1981. 111: Sun *et al.*, 1991. 112: Ding & Sun, 1980. 113: Prakash *et al.*, 1982. 114: Verma & Khetwal, 1985. 115: He *et al.*, 1984. 116: Hostettmann & Miura, 1977. 117: Hostettmann & Jacot-Guillarmod, 1976. 118: Haqqani, 1981. 119: Khetwal *et al.*, 1990. 120: Kulanthaivel *et al.*, 1988. 121: Bhan & Kalla, 1982. 122: Hu *et al.*, 1991. 123: Kanamori & Sakamoto, 1993. 124: Fukamiya *et al.*, 1990. 125: Ghosal *et al.*, 1974b. 126: Ghosal *et al.*, 1975c. 127: Ahmad *et al.*, 1973. 128: Chung *et al.*, 1986. 129: Tomimori & Komatsu, 1969. 130: Massias *et al.*, 1977. 131: Bisht *et al.*, 1991. 132: Khetwal & Bisht, 1988. 133: Agata *et al.*, 1981. 134: Neu *et al.*, 1991. 135: Liao *et al.*, 1991. 136: Lin *et al.*, 1987. 137: Lin *et al.*, 1982a. 138: Chen *et al.*, 1992. 139: Lin *et al.*, 1982b. 140: Lin *et al.*, 1984. 141: Yang & Zhou, 1980a. 142: Yang & Zhou, 1980b. 143: Yang *et al.*, 1995.

earlier in the tree, as shown by using a single oxidation at a time. Note that this postulated pathway does not require any reductions.

Similarly, the compounds **8a–8n** can be derived from **8**. In this case, however, it is position 7 in compound **8** which is inactive for oxidation. In analogy to the above, this position can be oxidized only after introduction of an oxygen at C-6 or C-8.

Using these principles, the double tree has been constructed. Only in a few cases can there be doubt about the placement of compounds with certain substitution patterns. Thus, **9d** could as well be derived from **8c** as from **9c** but it occurs in the same plants as the latter; similar arguments have been used for the other borderline cases.

Table 6.3 lists the occurrences of different types of xanthenes for the genera of Gentianaceae from which xanthenes have been reported. Based on these data, four groups of genera can be distinguished, showing the following characteristics:

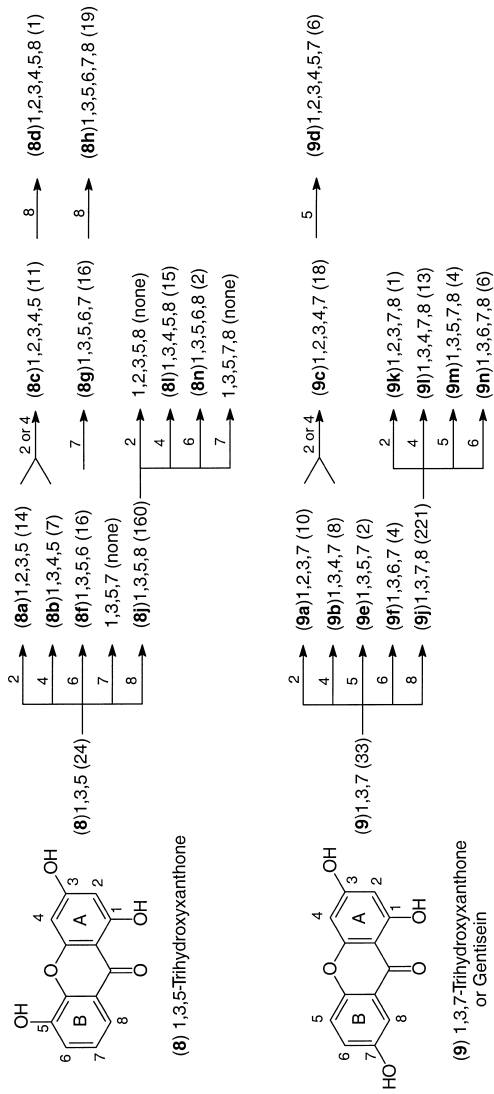


Figure 6.9. Presumed biosynthetic tree leading to substituted xanthenes in Gentianaceae. Bold numbers refer to a parent compound with the oxidation pattern indicated. Each parent compound represents all derivatives (methyl ethers, glycosides, etc.) reported to have this oxidation pattern. The number given in parentheses shows how many times compounds with this oxidation pattern have been reported. Numbers above product arrows show the position in which oxidation takes place to give the next product.

Table 6.3. The known occurrence of the different types of xanthonenes in genera of Gentianaceae

Genus	8 ^a	8a–8d	8f–8h	8j	8l	8n	9	9a–9d	9e	9f	9j	9k	9l	9m	9n
<i>Anthocleista</i> (1) ^b	—	—	—	—	—	—	—	—	—	—	3 ^c	—	—	—	—
<i>Blackstonia</i> (1)	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—
<i>Canscora</i> (1)	5	—	21	—	—	—	—	—	—	1	4	—	—	—	4
<i>Centaurium</i> (6)	—	—	14	7	—	2	—	—	—	—	7	—	—	—	—
<i>Chironia</i> (1)	6	—	6	—	—	—	1	—	—	—	4	—	—	—	—
<i>Comastoma</i> (1)	—	—	—	2	—	—	—	—	—	—	4	—	—	—	—
<i>Eustoma</i> (1)	1	—	2	—	—	—	1	—	—	—	1	—	—	—	—
<i>Frasera</i> (5)	2	12	—	3	—	—	3	14	—	—	—	—	—	—	—
<i>Gentiana</i> (29)	—	—	—	36	6	—	16	1	—	—	80	—	—	—	—
<i>Gentianella</i> (8)	—	—	—	21	7	—	1	—	—	—	9	—	4	—	—
<i>Gentianopsis</i> (12)	—	—	—	—	—	—	2	—	—	—	5	—	—	—	—
<i>Halenia</i> (4)	—	7	—	1	—	—	—	13	—	—	—	—	—	—	—
<i>Hoppea</i> (2)	2	—	6	—	—	—	—	—	2	—	1	—	—	—	—
<i>Ixanthus</i> (1)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2
<i>Lomatogonium</i> (2)	—	—	—	3	—	—	1	—	—	—	3	—	—	—	—
<i>Macrocarpaea</i> (1)	—	—	—	—	—	—	1	—	—	—	1	—	—	—	—
<i>Orphium</i> (1)	—	—	—	—	—	—	—	—	—	—	3	—	—	—	—
<i>Schultesia</i> (1)	2	2	1	1	—	—	—	—	—	—	3	—	—	—	—
<i>Swertia</i> (40)	6	10	—	86	2	—	7	6	—	—	92	1	6	4	—
<i>Tripterospermum</i> (2)	—	—	1	—	—	—	—	2	—	2	—	—	3	—	—
<i>Veratrilla</i> (1)	—	2	—	—	—	—	—	7	—	—	—	—	—	—	—

Notes:

^a Bold numbers refer to the compounds in Fig. 6.9.

^b Number of species investigated.

^c The values correspond to the number of compounds reported from each genus with the actual substitution pattern. If the same compound occurs in more than one species of the same genus, each occurrence has been counted.

- **group 1:** only **9** and/or the derived **9j** are present;
- **group 2:** predominance of 8-substitution with compounds derived from both **8** and **9**;
- **group 3:** predominance of 2- and/or 4-substitution, but never 6-substitution;
- **group 4:** predominance of 6-substitution.

In **group 1**, with only 1,3,7- (**9**) and/or 1,3,7,8-tetrasubstituted xanthonenes (**9j**), we have five genera: *Anthocleista*, *Blackstonia*, *Gentianopsis*, *Macrocarpaea*, and *Orphium*. This could be considered the most primitive state. It should be noted that except for *Gentianopsis*, these genera have been poorly sampled, with only a single species of each. (Also note that many

species of *Gentiana* and *Swertia* (Table 6.2) would belong here if they were the single example investigated from either genus!)

The genera in **group 2** could be seen as derived from those of **group 1** since they contain both the 1,3,5,8- and the 1,3,7,8-tetrasubstituted xanthenes (**8j** and **9j**), these being formed by an oxidation at position 8 of either of the basic structures **8** or **9**. These types of xanthenes occur sporadically in many genera, but they are not predominant in all. The genera in this group are *Comastoma*, *Gentiana*, *Gentianella*, *Lomatogonium*, and *Swertia*. This could be considered an intermediate degree of biosynthetic advancement. *Tripterospermum* may also belong in this group (see below).

In **group 3**, the 2- and/or 4-substituted xanthenes (**8a–8d**, **9a–d**, **8l**, and **9l**) are the most common. The taxa of this group produce mainly the hexa-substituted compounds which demand the most oxidation steps, and they may be considered the most advanced. Group 3 includes the genera *Fraseria*, *Halenia*, and *Veratrilla*. Nine of the 34 investigated *Swertia* species and five of the eight investigated *Gentianella* species also have some of these compounds present, but usually in admixture with the typical compounds from the group 2 taxa. Therefore, *Swertia* and *Gentianella* could be intermediates between these two groups. *Tripterospermum* is a special case. Two species have been investigated (Table 6.3), and in these were found the compounds **8f** and **9f** (6-substitution, three findings), which are otherwise characteristic for group 4. However, the remaining compounds in this genus, namely **9b** and **9l** (4-substitution, five findings), are elsewhere encountered mainly in *Swertia* and *Gentianella* on the one hand, and in group 3 on the other. Therefore, *Tripterospermum* is either an intermediate between groups 2 and 3, or could belong to group 4.

Compounds derived mainly by oxidation at the 6-position of **8** are the most common trait in the xanthenes of **group 4** taxa. In these genera, the compounds **8f–8h**, **8n**, **9f**, and **9n** are present. This is another advanced group with many poly-substituted compounds. It includes *Canscora*, *Centaurium*, *Chironia*, *Eustoma*, *Hoppea*, and *Ixanthus*. With some reservations, we have also placed the genus *Schultesia* here. Although 6-substitution is not the predominant feature, it is still present, but the sampling is poor since only a single species has been investigated. As discussed above, *Tripterospermum* could also belong here.

It should be emphasized that the above division has been based on the reported isolations. For some genera only a single species has been investigated and only few xanthenes have been isolated. For example, in *Blackstonia* only a single species was investigated and only a single compound was reported. A more thorough investigation of individual genera

might lead to different conclusions. Despite this, a large number of compounds have now been isolated from many taxa, and we believe that the data can be given some credence. However, the inherent problem with chemical data is that lack of compounds is only rarely reported; usually this happens only in reports of systematic work.

Comparing the above data with the strict consensus tree presented by Struwe *et al.* (1998, 2002: Figs. 2.1–2.3) based on molecular data (*trnL* intron and *matK* sequences), we see some interesting and strong correlations with the six major clades of Gentianaceae. To clarify the distribution patterns of the compounds, we have listed the sequenced genera within each tribe and shown the distribution of the compounds found in each genus (Table 6.4). For the xanthonenes, this is done indirectly because of the way they have been used to classify the genera above into four groups with different biosynthetic potential.

Notably, no xanthonenes have so far been reported from the Exaceae. However, it appears that only one genus of this clade, *Exacum*, has been investigated chemically (see Table 6.1), and further research may reveal the presence of xanthonenes also in this group.

The genera of **group 1**, with their poor sampling (usually a single species in each genus) and with only a few biosynthetically primitive compounds reported from each, are randomly found in the remaining clades (tribes). The genera of **group 2**, however, with xanthonenes that can be considered more advanced than those from group 1, all belong to the Gentianeae. *Tripterospermum*, which as discussed above has an ambiguous position with regard to chemistry, was not sampled in the work by Struwe *et al.* (1998). However, it is known from another nuclear DNA sequencing work (Yuan & Küpfer, 1995) that this genus belongs in tribe Gentianeae, and therefore it has been included in Table 6.4.

Within the Gentianeae further specialization in xanthone biosynthesis has taken place in the genera of **group 3**, which comprise *Frasera*, *Halenia*, and *Veratrilla*. The relationships of these genera with other genera of sub-tribe Swertiinae are unresolved in the strict consensus tree (Struwe *et al.*, 1998: fig. 1, 2002: Fig. 2.1), but the xanthonenes support a close relationship between the three genera *Frasera*, *Halenia*, and *Veratrilla* – with *Gentianella* and *Swertia* as probable intermediates to the remaining genera in tribe Gentianeae.

Finally, the taxa of **group 4** (including the chemotaxonomically more dubious *Schultesia*) have specialized in producing 6-substituted xanthonenes and are all members of the Chironieae.

In conclusion, the xanthone distribution data in Gentianaceae show a very

Table 6.4. The distribution of chemical characters in the genera for which sequence data were presented by Struwe et al. (1998) and Thiv et al. (1999)

Tribe ^a	Genus	Secoiridoids ^b	Xanthone data ^c	Mangiferin	C-Glucoflavones
Saccifolieae	<i>Saccifolium</i>				
Exaceae	<i>Exacum</i>	x			
Exaceae	<i>Ornichia^d</i>				
Exaceae	<i>Sebaea^d</i>				
Exaceae	<i>Tachiadenus^d</i>				
Chironieae	<i>Blackstonia</i>	x	Group 1		
Chironieae	<i>Canscora</i>		Group 4	x	
Chironieae	<i>Centaurium</i>	x	Group 4		
Chironieae	<i>Chironia</i>	x	Group 4		
Chironieae	<i>Cicendia</i>	x			
Chironieae	<i>Coutoubea</i>	x			
Chironieae	<i>Deianira^d</i>				
Chironieae	<i>Eustoma</i>	x	Group 4		
Chironieae	<i>Geniostemon</i>				
Chironieae	<i>Hoppea</i>		Group 4	x	
Chironieae	<i>Ixanthus</i>	x	Group 4		
Chironieae	<i>Orphium</i>		Group 1		
Chironieae	<i>Sabatia</i>	x			
Chironieae	<i>Schinziiella^d</i>				
Chironieae	<i>Schultesia</i>	x	Group 4		
Chironieae	<i>Symphyllophyton^d</i>				
Chironieae	<i>Xestaea^d</i>				
Helieae	<i>Calolisianthus^d</i>				
Helieae	<i>Chelonanthus</i>	x			
Helieae	<i>Irlbachia</i>				
Helieae	<i>Macrocarpaea</i>		Group 1		
Helieae	<i>Neblinantha^d</i>				
Helieae	<i>Symbolanthus^d</i>				
Helieae	<i>Tachia^d</i>				
Helieae	<i>Tetrapollinia^d</i>				
Helieae	<i>Wurdackanthus^d</i>				
Potalieae	<i>Anthocleista</i>	x	Group 1		
Potalieae	<i>Djaloniella^d</i>				
Potalieae	<i>Enicostema</i>	x			x
Potalieae	<i>Fagraea</i>	x			x
Potalieae	<i>Faroa</i>	x			
Potalieae	<i>Lisianthus</i>	x			
Potalieae	<i>Neurotheca^d</i>				
Potalieae	<i>Potalia</i>	x			x
Potalieae	<i>Pycnosphaera^d</i>				
Potalieae	<i>Urogentias^d</i>				
Gentianeae	<i>Bartonia</i>				
Gentianeae	<i>Comastoma</i>		Group 2		
Gentianeae	<i>Frasera</i>		Group 3		x
Gentianeae	<i>Gentiana</i>	x	Group 2	x	x
Gentianeae	<i>Gentianella</i>	x	Group 2	x	x
Gentianeae	<i>Gentianopsis</i>		Group 1	x	x
Gentianeae	<i>Halenia</i>	x	Group 3		

Table 6.4. (cont.)

Tribe ^a	Genus	Secoiridoids ^b	Xanthone data ^c	Mangiferin	C-Glucoflavones
Gentianeae	<i>Jaeschkea</i> ^d				
Gentianeae	<i>Lomatogonium</i>	x	Group 2		x
Gentianeae	<i>Megacodon</i> ^d				
Gentianeae	<i>Obolaria</i> ^d				
Gentianeae	<i>Swertia</i>	x	Group 2	x	x
Gentianeae	<i>Tripterospermum</i> ^e		Group 2(4)	x	
Gentianeae	<i>Veratrilla</i>		Group 3		

Notes:

^a Classification according to Struwe *et al.* (2002).

^b Mainly the secoiridoids swertiamarin (6) and gentiopicroside (7).

^c The derived data; the groups are of genera with similar compounds present (see text).

^d These genera have apparently not been chemically investigated.

^e This genus was not sequenced by Struwe *et al.* (1998), but is known to belong to the same clade as *Gentiana* (Yuan & Küpfer, 1995).

good correlation with the phylogenetic results obtained from DNA sequence data. Further research on xanthones in genera uninvestigated thus far will probably prove to be very useful for chemosystematic work in the family.

MANGIFERIN

Mangiferin (10; Fig. 6.10) was first isolated from *Mangifera indica* (Anacardiaceae). In the figure, the structure is shown upside down compared with the xanthone structures in Figs. 6.8 and 6.9 in order to demonstrate the different biosynthetic relationship. Mangiferin is a so-called C-glucoxanthone since the sugar is attached to the xanthone nucleus by a carbon-carbon (C-C) bond. C-Glucosides are resistant to hydrolysis, in contrast to the more common O-glucosides, in which the sugar is attached by a carbon-oxygen (C-O) bond. The latter renders the compound hydrolyzable by enzymes or by acid catalysis to give the free sugar and the aglucone. Thus, C-glucosides are easily detected by chromatographic analysis of hydrolyzed plant extracts since they retain the sugar moiety after acid hydrolysis and consequently have special chromatographic properties compared with other phenolic plant constituents. Only a few compounds belong to this group, and mangiferin is by far the most widespread. In a review on the distribution of the C-glycoxanthones known at that time, Richardson (1983) found that mangiferin occurred more or less sporadically in 60 species, 18 genera, and 13 families of dicots (it is also present in monocots and in ferns). Of these,

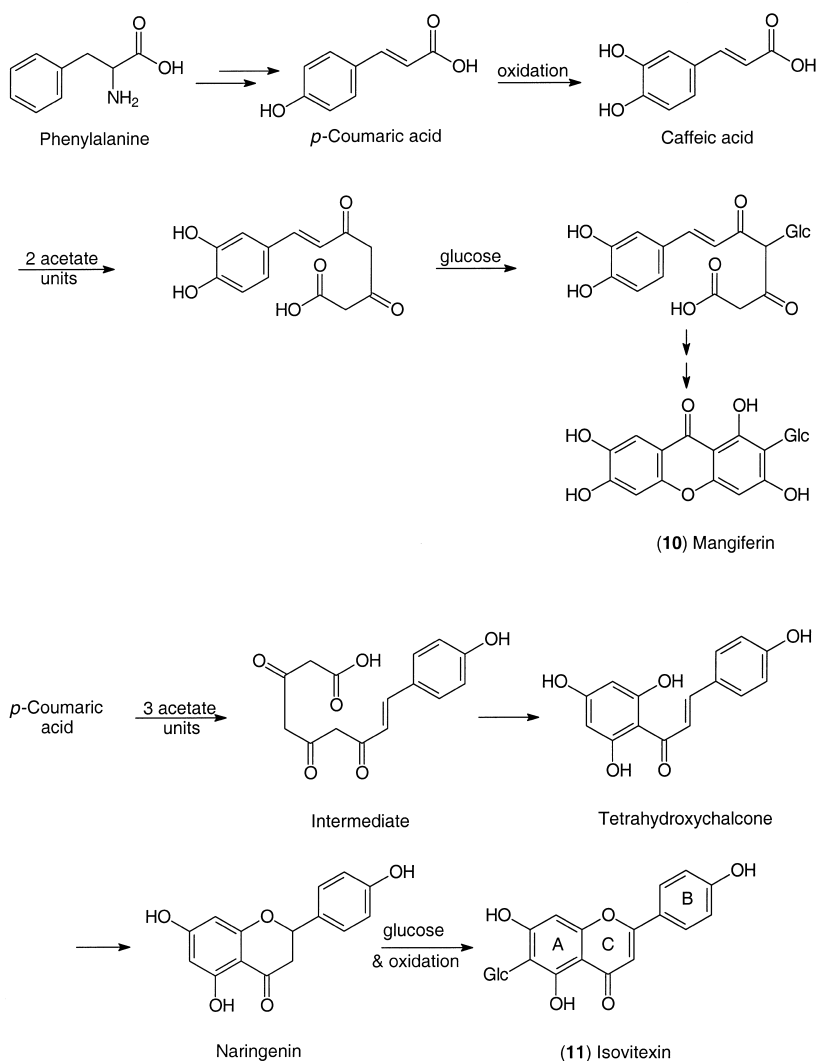


Figure 6.10. Biosynthetic pathways leading to mangiferin (10) and the C-glucoflavone isovitexin (11); note the common precursors.

Leguminosae (18 species and two genera) and Gentianaceae (23 species and three genera) appeared to be the main centers of distribution for this type of compound. Richardson noted that mangiferin was often found together with C-glucoflavones, but claimed that the compound was apparently of little chemotaxonomic significance.

Biosynthesis

The biosynthesis of the C-glucoside mangiferin (**10**) has been investigated in *Anemarrhena asphodeloides* (Liliaceae) with a result somewhat different from that found for the other xanthenes (Fujita & Inoue, 1980). In this plant, all the carbon atoms of phenylalanine (Fig. 6.10) as well as of cinnamic and *p*-coumaric acid are incorporated into the xanthone nucleus, and benzoic acid is apparently not on the pathway. Thus we have a pathway for the formation of mangiferin which is distinct from that of the normal xanthenes. This could of course be an example of a different pathway in a completely different taxon, but the oxidation pattern found in mangiferin is not the same as that seen in most of the other xanthenes so far isolated from Gentianaceae, consistent with a different biosynthetic pathway as discussed below. As seen from Fig. 6.10, the pathway leading to **10** is more related to that found for the C-glucoflavones (e.g., isovitexin) than to that of the normal xanthenes.

Results

Mangiferin (**10**) has so far been recorded in 42 species and seven genera within Gentianaceae (Table 6.5), almost a doubling since the review of Richardson (1983). The records in Table 6.5 include two O-glucosides of **10** in *Gentiana asclepiadea* (Goetz & Jacot-Guillarmod, 1977), but unlike the iridoids and the C-glucoflavones, **10** is not usually found in esterified form.

Also unlike the iridoids, mangiferin (**10**) is not consistently present in all the species of Gentianaceae investigated. Thus, in a chemotaxonomic investigation (Massias *et al.*, 1982), **10** was detected in 15 of the 18 species studied. In a similar study (Hostettmann-Kaldas *et al.*, 1981), **10** was found to occur in about half the 17 species studied.

The above data have also been listed in Table 6.4, and again we see some interesting correlations, despite the fact that only a limited number of genera have been reported to contain mangiferin. This compound has not so far been reported from the Exaceae. By far the largest number of reports are from *Gentiana*, *Gentianella*, *Gentianopsis*, *Swertia*, and *Tripterispermum*, all of which are well sampled and belong to the Gentianeae. The remaining two reports are from a single species each of *Canscora* and *Hoppea*, both of which belong to the Chironieae.

C-GLUCOFLAVONES

As in mangiferin (**10**), the sugar in C-glucoflavones is attached to the flavonoid nucleus by a C–C bond and these compounds are therefore much

Table 6.5. *The known occurrence of mangiferin in Gentianaceae*

Taxon	Reference
<i>Canscora decussata</i>	Ghosal & Chaudhuri, 1975
<i>Fagraea blumei</i>	Cuendet <i>et al.</i> , 1997
<i>Gentiana asclepiadea</i>	Goetz & Jacot-Guillarmod, 1977
<i>Gentiana campestris</i>	Kaldas <i>et al.</i> , 1975
<i>Gentiana corymbifera</i>	Massias <i>et al.</i> , 1981
<i>Gentiana cruciata</i>	Goetz <i>et al.</i> , 1976
<i>Gentiana favrati</i>	Hostettmann & Jacot-Guillarmod, 1977
<i>Gentiana karelinii</i>	Butayarov <i>et al.</i> , 1993a
<i>Gentiana lactea</i>	Schaufelberger & Hostettmann, 1988
<i>Gentiana lutea</i>	Bellmann & Jacot-Guillarmod, 1973
<i>Gentiana marcaillhouana</i>	Luong <i>et al.</i> , 1980
<i>Gentiana nivalis</i>	Hostettmann & Jacot-Guillarmod, 1977
<i>Gentiana orbicularis</i>	Massias <i>et al.</i> , 1982
<i>Gentiana pneumonanthe</i>	Hostettmann-Kaldas <i>et al.</i> , 1981
<i>Gentiana schistocalyx</i>	Nikolaeva <i>et al.</i> , 1980c
<i>Gentiana utriculosa</i>	Hostettmann & Jacot-Guillarmod, 1977
<i>Gentiana verna</i>	Hostettmann & Jacot-Guillarmod, 1974
<i>Gentianella campestris</i>	Massias <i>et al.</i> , 1982
<i>Gentianella caucasica</i>	Lubsandorzheva <i>et al.</i> , 1986
<i>Gentianella germanica</i>	Hostettmann-Kaldas & Jacot-Guillarmod, 1978
<i>Gentianella ramosa</i>	Hostettmann-Kaldas & Jacot-Guillarmod, 1978
<i>Gentianella serotina</i>	Massias <i>et al.</i> , 1982
<i>Gentianella stenocalyx</i>	Massias <i>et al.</i> , 1982
<i>Gentianopsis</i> (12 species)	Massias <i>et al.</i> , 1982
<i>Hoppea dichotoma</i>	Ghosal <i>et al.</i> , 1978a
<i>Swertia calycina</i>	Rodriguez <i>et al.</i> , 1995a
<i>Swertia chirata</i>	Ghosal <i>et al.</i> , 1973b
<i>Swertia connata</i>	Solov'eva <i>et al.</i> , 1980b
<i>Swertia cordata</i>	Atta-ur-Rahman <i>et al.</i> , 1994
<i>Swertia dilatata</i>	Tomimori <i>et al.</i> , 1974
<i>Swertia elongata</i>	Kong <i>et al.</i> , 1995
<i>Swertia franchetiana</i>	Ding <i>et al.</i> , 1988
<i>Swertia gracilescens</i>	Tomimori <i>et al.</i> , 1974
<i>Swertia macrosperma</i>	Zhou & Liu, 1990
<i>Swertia mussotii</i>	Ding & Sun, 1980
<i>Swertia perennis</i>	Hostettmann & Jacot-Guillarmod, 1976
<i>Swertia perfoliata</i>	Haqqani, 1981
<i>Swertia randaiensis</i>	Tomimori & Komatsu, 1969
<i>Swertia speciosa</i>	Massias <i>et al.</i> , 1977
<i>Swertia swertopsis</i>	Tomimori & Komatsu, 1969
<i>Swertia tosaensis</i>	Tomimori & Komatsu, 1969
<i>Tripterospermum lanceolatum</i>	Lin <i>et al.</i> , 1982a
<i>Tripterospermum taiwanense</i>	Lin <i>et al.</i> , 1984

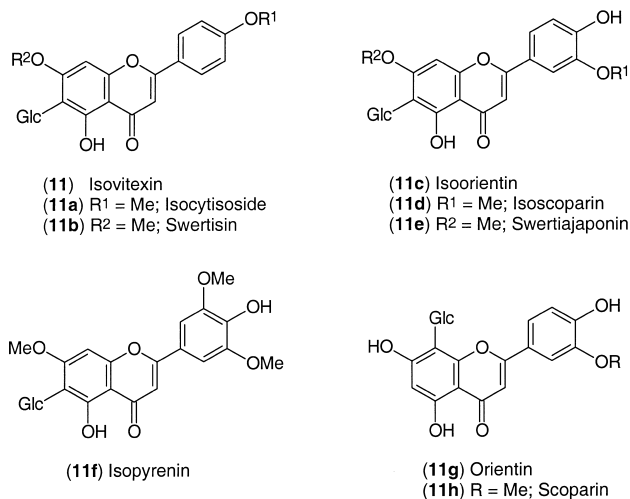


Figure 6.11. C-Glucoflavones reported from Gentianaceae.

more stable than the common O-glucosides. C-Glucoflavones are widely distributed in monocots (see Harborne *et al.*, 1975), but are more scattered in dicots, being found mainly in Leguminosae, Gentianaceae, and Asteraceae. In Gentianaceae, the compounds were at that time (1975) known from six species of *Swertia* and eight species of *Gentiana*. C-Glucoflavones are usually found as such in the plants, but we have seen several reports of C-glucoflavones derivatized with additional O-glycosylation or as esters. However, these reports are very scattered, and we have merely recorded the presence of the parent compounds and their methyl ethers. The structures of the nine compounds so far isolated from the family are depicted in Fig. 6.11 (11–11h).

Biosynthesis

Flavonoids in plants are, like the normal xanthenes, formed via a mixed shikimate–acetate pathway. However, the detailed pathway is entirely different since the complete carbon skeleton of phenylalanine is retained in the end-product. First, the phenylalanine is transformed to cinnamic acid and then further oxidized to *p*-coumaric acid as shown (Fig. 6.10). Condensation of *p*-coumaric acid with three acetate units gives first an intermediate which by ring-closure forms the A-ring to provide a tetrahydrochalcone. Another ring-closure to form the central C-ring gives rise

to the flavanone naringenin. This pathway is apparently also valid for the formation of C-glucoflavones in Gentianaceae. Thus, Fujita and Inoue (1979) fed radiolabeled precursors to *Swertia japonica* and got similar results in the biosynthesis of isovitexin (**11**), swertisin (**11b**), isoorientin (**11c**), and swertia-japonin (**11e**) – the route is given here only for the first compound. This shows that the sugar is probably attached at the flavanone stage, which is then transformed to the corresponding flavone found in the plant, namely **11**. The analogy to the biosynthesis of mangiferin is obvious, except that in the latter case only two acetate units are incorporated in the intermediate before cyclization. Note that in both cases all the hydroxy groups in the product stem from oxygen atoms originally present in the precursor.

Results

We have recorded C-glucoflavones in 78 species in nine genera (Table 6.6). Systematic surveys of *Gentiana*, *Gentianella*, *Gentianopsis*, and *Swertia*, which have been investigated most intensively, indicate that these compounds may be generally present, at least in parts of Gentianeae. Thus they were found in all of the 22 *Gentiana* species examined by Hostettmann *et al.* (1975) and Hostettmann-Kaldas *et al.* (1981), as well as in the 17 species from the first three of the above-mentioned genera examined by Massias *et al.* (1982). Similarly, they were found in all five species of *Swertia* investigated by Komatsu *et al.* (1968).

From the data in Table 6.6 it appears that the two biosynthetically primary compounds isovitexin (**11**) and isoorientin (**11c**) are by far the most common in the family. Increasing O-methylation has been linked to advancement of the plant taxa (Harborne, 1977), and presence of the methyl ethers **11a/11b** and **11d/11e** may thus be taken as an indication of this (Massias *et al.*, 1982).

When we combine the data from Table 6.6 into the table of sequenced taxa (Table 6.4) we again find an interesting correlation. C-Glucoflavones appear to be very common in the Gentianeae, where they have been reported from *Frasera*, *Gentiana*, *Gentianella*, *Gentianopsis*, *Lomatogonium*, and *Swertia*. The remaining reports are from a single species each of *Enicostema*, *Fagraea*, and *Potalia*, all of which belong to the Potalieae. Despite the poor sampling, it may be significant that no methyl ethers have been reported from this tribe.

Unfortunately, systematic investigations have been performed only in genera of the Gentianeae. It would be interesting to know if the compounds are consistently present in other genera.

Table 6.6. *The known occurrence of C-glucoflavones in Gentianaceae*

Taxon	Compounds ^a		References ^b	
<i>Enicostema hyssopifolium</i>	11	11b		1
<i>Frasera tetrapetala</i>		11b		2
<i>Gentiana affinis</i>		11c		3
<i>Gentiana algida</i>		11c	11g	3, 4
<i>Gentiana argentea</i>	11	11c		5
<i>Gentiana arisanensis</i>		11c		6
<i>Gentiana asclepiadea</i>	11	11c		7
<i>Gentiana bavarica</i>	11	11c		8
<i>Gentiana brachyphylla</i>	11	11c		8
<i>Gentiana burseri</i>	11	11c		9
<i>Gentiana calycosa</i>		11c		3
<i>Gentiana campestris</i>		11b		10, 11
<i>Gentiana cerastioides</i>		11c		3
<i>Gentiana ciliata</i>	11	11c	11d	12
<i>Gentiana corymbifera</i>	11	11b	11c	13
<i>Gentiana depressa</i>	11	11c		14
<i>Gentiana detonsa</i>		11c		3
<i>Gentiana elwesii</i>	11	11c		14
<i>Gentiana farreri</i>		11c	11d	15
<i>Gentiana favrati</i>	11	11c		8
<i>Gentiana karelinii</i>		11c		16
<i>Gentiana lactea</i>	11	11c		17
<i>Gentiana lutea</i>	11	11c		18
<i>Gentiana macrophylla</i>	11	11c		19
<i>Gentiana marcaillhouana</i>	11	11c		20, 21
<i>Gentiana nivalis</i>	11	11c		3
<i>Gentiana olivieri</i>		11c	11g	22
<i>Gentiana orbicularis</i>		11c		23
<i>Gentiana pannonica</i>	11	11c		9
<i>Gentiana pedicellata</i>	11	11c		14
<i>Gentiana pneumonanthe</i>	11		11d	11h
<i>Gentiana prolata</i>	11	11c		14
<i>Gentiana punctata</i>	11	11c	11d	25
<i>Gentiana purpurea</i>	11	11c		9
<i>Gentiana pyrenaica</i>	11	11a	11d	11f
<i>Gentiana rostani</i>	11	11c		8
<i>Gentiana schistocalyx</i>	11			27
<i>Gentiana schleicheri</i>	11	11c		8
<i>Gentiana sikkimensis</i>	11	11c		14
<i>Gentiana sino-ornata</i>		11c		15
<i>Gentiana strictiflora</i>		11c		3
<i>Gentiana utriculosa</i>	11	11c		8
<i>Gentiana verna</i>		11c		28
<i>Gentiana villarsii</i>	11	11c		9
<i>Gentianella azurea</i>		11c		29
<i>Gentianella campestris</i>		11b	11c	23

Table 6.6. (cont.)

Taxon	Compounds ^a				References ^b
<i>Gentianella germanica</i>		11b	11c		30
<i>Gentianella ramosa</i>		11b	11c		30
<i>Gentianella serotina</i>		11b	11c		23
<i>Gentianella stenocalyx</i>	11		11c		23
<i>Gentianopsis</i> (11 species)	11		11c	11d	23
<i>Lomatogonium carinthiacum</i>			11c		31
<i>Lomatogonium rotatum</i>			11c		32
<i>Potalia amara</i>		11b			33
<i>Swertia alata</i>		11b			34
<i>Swertia bimaculata</i>	11				35
<i>Swertia diluta</i>	11				35
<i>Swertia franchetiana</i>		11b			36
<i>Swertia japonica</i>	11	11b	11c	11e	35, 37
<i>Swertia mussotii</i>		11b			38
<i>Swertia paniculata</i>		11b	11c		39
<i>Swertia perennis</i>	11		11c		40
<i>Swertia pseudochinensis</i>	11				35
<i>Swertia purpurascens</i>		11b			41
<i>Swertia randaiensis</i>	11				35
<i>Swertia swertopsis</i>	11		11c		42

Notes:^a Bold numbers refer to the compounds in Fig. 6.11.^b References: 1: Ghosal & Jaiswal, 1980. 2: Agata *et al.*, 1984. 3: Hostettmann-Kaldas *et al.*, 1981. 4: Tan *et al.*, 1996. 5: Chulia & Debelmas, 1977. 6: Kuo *et al.*, 1996. 7: Goetz & Jacot-Guillarmod, 1977. 8: Hostettmann & Jacot-Guillarmod, 1977. 9: Hostettmann *et al.*, 1975. 10: Kaldas *et al.*, 1974. 11: Kaldas *et al.*, 1975. 12: Goetz *et al.*, 1978. 13: Massias *et al.*, 1981. 14: Chulia & Debelmas, 1977. 15: Schaufelberger & Hostettmann, 1987. 16: Butayarov *et al.*, 1993a. 17: Schaufelberger & Hostettmann, 1988. 18: Bellmann & Jacot-Guillarmod, 1973. 19: Tikhonova *et al.*, 1989. 20: Luong *et al.*, 1981. 21: Luong *et al.*, 1980. 22: Ersoz & Calis, 1991. 23: Massias *et al.*, 1982. 24: Burret *et al.*, 1978. 25: Luong & Jacot-Guillarmod, 1977. 26: Marston *et al.*, 1976. 27: Nikolaeva *et al.*, 1980c. 28: Hostettmann & Jacot-Guillarmod, 1974. 29: Zhang & Yang, 1994. 30: Hostettmann-Kaldas & Jacot-Guillarmod, 1978. 31: Schaufelberger & Hostettmann, 1984. 32: Khishgee & Pureb, 1993. 33: S. R. Jensen & J. Schripsema, unpubl. 34: Khan *et al.*, 1979. 35: Komatsu *et al.*, 1968. 36: Ding *et al.*, 1988. 37: Kubota *et al.*, 1983. 38: Sun *et al.*, 1991. 39: Verma & Khetwal, 1985. 40: Hostettmann & Jacot-Guillarmod, 1976. 41: Miana, 1973. 42: Tomimori & Komatsu, 1969.

PHYTOCHEMICAL CONCLUSIONS

The family Gentianaceae is apparently characterized by the universal occurrence of iridoid glucosides. The iridoids found are consistently seco-iridoids; the occasional carbocyclic iridoids present are on the biosynthetic pathway leading to the secoiridoids (Fig. 6.1). Secoiridoids are characteristic for the whole order Gentianales and are hardly ever present in Scrophulariales/Lamiales, where iridoid glucosides of an alternative biosynthetic pathway are frequent. We have recorded *c.* 90 different iridoid compounds from the family (Figs. 6.2–6.7), from 127 species in 24 genera (Table 6.1). However, the most common iridoid glucosides present are those represented by the sequence sweroside (**5**), swertiamarin (**6**), and gentiopicroside (**7**). The last two are found almost exclusively in Gentianaceae, and are reported from 107 of the 127 species listed in Table 6.1. The iridoid glucosides are frequently found as the parent compounds above, but also often occur as derivatives, e.g., esterified with acid moieties, of which many are unique to the Gentianaceae.

Xanthonenes are also present in many species, although they are not universal in the family. About 100 different compounds are reported from 110 species in 21 genera. Using a biosynthetic scheme based partly on actual experiments (Fig. 6.8) and partly on deductions from structural features, the xanthonenes have been arranged according to biosynthetic complexity and to oxidation pattern (Fig. 6.9; Table 6.3). The genera have then been classified into groups according to the compounds present, and these groups provide a good fit with the clades indicated from phylogenetic results based on *trnL* intron and *matK* sequences (Struwe *et al.*, 2002).

The C-glucoxanthone mangiferin (Table 6.5) has a more limited distribution than the iridoids and the normal xanthonenes. The compound has been reported from 42 species in seven genera, and it appears to be present only in two of the above groups.

The C-glucoflavones are much less variable than the iridoids and the xanthonenes; only nine different compounds have been reported so far from a total of 78 species in nine genera (Table 6.6). This group of compounds also has a limited distribution in the family, and is again found in only two of the above groups.

Combining the known chemical data and the sequence data (Table 6.4), we can now list the chemical characteristics of the tribes of Gentianaceae. A question mark indicates that data are available but scarce. The “absent” character is unfortunately very uncertain, since it may merely mean lack of data.

Saccifolieae:

Not investigated

Exaceae:

Secoiridoids (including **6** and **7**): present

Xanthonenes: absent

Mangiferin: absent

C-Glucoflavones: absent

Chironieae:

Secoiridoids (including **6** and **7**): present

Xanthonenes: 6-substituted but not 4-substituted are present

Mangiferin: present (?)

C-Glucoflavones: absent

Helieae:

Secoiridoids (including **6** and **7**): present

Xanthonenes: only primitive ones are present (?)

Mangiferin: absent

C-Glucoflavones: absent

Potalieae:

Secoiridoids (including **6** and **7**): present

Xanthonenes: only primitive ones are present (?)

Mangiferin: absent

C-Glucoflavones: present (?)

Gentianeae:

Secoiridoids (including **6** and **7**): present

Xanthonenes: 8-substituted or 2- and 4-substituted predominant

Mangiferin: present

C-Glucoflavones: present

SOME PHARMACOLOGICAL REMARKS ON THE GENTIANACEAE

Plants from the Gentianaceae are best known for their bitter taste, which can be related to their content of iridoids, such as amarogentin (**5d**), the most bitter compound known. Bitters have been traditional remedies for loss of appetite and fever, and are still included in many “tonic” formulations (Martindale, 1982). Various herbs from the Gentianaceae are common in pharmacopoeias: centaury (the dried flowering tops of the common centaury, *Centaureum erythraea*, and other species of *Centaureum*), chirata (the dried plant *Swertia chirata*, collected when in flower), and gentian (the dried, partially fermented rhizome and root of *Gentiana lutea*). Many other

species from the family have been used for the same purpose in various regions of the world, e.g., *Chironia baccifera* in South Africa, *Erythraea chilensis* in Chile and Peru, *Coutoubea spicata* in Brazil, *Enicostema littorale* in India, *Frasera caroliniensis* in the USA, *Schultesia guianensis* in Central America, and *Centaurium australe* in Australia (Hegnauer, 1966).

Some specific activities have been reported for iridoids from Gentianaceae. Swertiamarin (**6**) should have anticholinergic properties (Bhattacharya *et al.*, 1976; Liang *et al.*, 1982; Yamahara *et al.*, 1991). For sweroside (**5**) and gentiopicroside (**7**) hepatoprotective activities have been reported (Zhou, 1991; Kondo *et al.*, 1994), and both compounds are being used as anti-hepatitis drugs.

Xanthones (especially mangiferin) are reported to give CNS stimulation (Bhattacharya *et al.*, 1972; Lin *et al.*, 1984), and this effect can be explained by their MAO inhibitory activity (Schaufelberger & Hostettmann, 1988). They should also have anti-inflammatory activity (Mandal *et al.*, 1992b). For bellidifolin and swerchirin a strong hypoglycemic activity has been reported (Saxena & Mukherjee, 1992; Saxena *et al.*, 1993; Basnet *et al.*, 1994, 1995). Norathyriol, a xanthone from *Tripterospermum*, was reported to have anti-inflammatory and analgesic activities. An investigation suggested that norathyriol might be a dual, but weak, cyclo-oxygenase and lipoxygenase pathway blocker (Wang *et al.*, 1994a). Norathyriol also suppressed inflammation-related edema, probably due partly to suppression of mast cell degranulation and hence reduction in the release of chemical mediators which increase vascular permeability, and partly, at least in higher doses, to protection of the vasculature from challenge by various mediators (Wang *et al.*, 1994b).

Flavan glucosides (from *Hoppea dichotoma*) are reported to have a sedative effect (Ghosal *et al.*, 1985). Antipsychotic activity has been reported for gentianine (Bhattacharya *et al.*, 1974), which antagonized amphetamine and decreased aggressiveness. Gentianadine decreased arterial pressure and had anti-inflammatory activity (Sadritdinov & Tulyaganov, 1972). An antifungal effect has been reported for anofinic acid and fomannoxin (Tan *et al.*, 1996) and for 2-methoxy-1,4-naphthoquinone (Rodriguez *et al.*, 1995a). Antifungal phosphocholine derivatives were extracted from *Irlbachia alata* (= *Chelonanthus alatus*; Tempesta *et al.*, 1994; Bierer *et al.*, 1995). In addition, a crude extract of *Swertia* with insect repellent activities has been reported (Okada, 1977).

Finally, swertifranchesinde was found to be a potent inhibitor of the DNA polymerase activity of HIV-1 reverse transcriptase (Pengsuparp *et al.*, 1995), and five tetrahydroxanthones isolated from *Tripterospermum lanceolatum* were shown to have a strong inhibitory effect on the activity of

Moloney murine leukemia virus reverse transcriptase (Chang *et al.*, 1992). The tetrahydroxyxanthenes also inhibited angiotensin-1-converting-enzyme (ACE) activity in a dose-dependent manner (Chen *et al.*, 1992).

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